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Original Communications

OBSERVATIONS ON CHANGES IN VENTRICULAR COMPLEXES PRODUCED BY BUNDLE BRANCH BLOCK WITH SPECIAL REFERENCE TO THE HYPOTHESIS OF ELECTRICAL AXIS AND THE CONCEPT OF DEXTROCARDIOGRAM AND LEVOCARDIOGRAM

CHARLES C. WOLFERTH, M.D., AND MARY M. LIVEZEY, M.D.
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WE HAVE previously reported results of electrocardiographic experiments that cast doubt on the validity of some of the underlying assumptions essential to the formulation of Einthoven's classic equilateral triangle hypothesis.[1-4] Moreover, results obtained by the method of balanced potentials and by placing the reference electrode over the spine of the right scapula led us to conclude that certain parts of the left ventricle tend to exert a greater influence in shaping the ventricular complexes of limb leads than other parts of the ventricular myocardium. As a matter of fact it would be difficult to avoid that conclusion even without special methods of pairing electrodes, provided one merely observes the effects of infarction in various parts of the left ventricle upon supposed electrical axis. Such observations must inevitably lead one to question the hypothesis of electrical axis as it is applied to the interpretation of electrocardiograms. The method of balanced potentials is the only procedure for which there is experimental evidence that the objective of reducing interference with the potential variations of the exploring electrode can be achieved in electrocardiograms; therefore the error involved in using this method to study distribution of potential on body surfaces should be less than that of other methods. It is desirable, nevertheless, to study the problem of electrical axis by some procedure that does not involve a matter still so controversial as the merit of methods of pairing electrodes.

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It occurred to us that analysis of the changes that occur in ventricular complexes as a result of human bundle branch block might offer an opportunity to test current views regarding electrical axis and Lewis' views regarding the human dextrocardiogram and levocardiogram, which he developed on the basis of his studies of canine bundle branch block, and which he tried to explain on the basis of his unquestioning acceptance of the hypothesis of electrical axis.[5] That is the purpose of this report. We accept Wilson and associates' classification of human right and left bundle branch block[6] rather than that of Lewis and his predecessors. The former is completely supported, at least as far as what is now called left bundle branch block is concerned, by the observations of Wolferth and Margolies[7] on the time relationships of various right and left ventricular events in bundle branch block. For this reason and others that will be discussed later, it seems clear that although there is little reason to question the correctness of Lewis' ideas as to the side of the lesion in experimental canine bundle branch block, he was led into error in his considerations of human bundle branch block. An attempt will be made to analyze the contributions of the right and left ventricle to various electrocardiographic leads in the human being.

The term dextrocardiogram is used to refer (in whatever lead is under consideration) to that part of the pattern of differences of potential which is presumably derived from electrical activity in the right ventricle and the part of the septum activated via the right ventricle. The term levocardiogram is used to refer similarly to the left ventricle and the part of the septum activated via the left side. These definitions correspond in one sense to Lewis' terms, true dextrogram and true levogram. We wish to avoid the connotation that the dextrocardiogram and levocardiogram necessarily reflect rotation of a supposed electrical axis in the right and left ventricles. Their values in any lead must obviously depend upon the contribution of each of the ventricles to the mean potential variations of the two (or more) positions in contact with the electrodes used to make a lead, irrespective of the mechanisms involved in the development of the potential variations.

When bundle branch block develops it may be assumed that intraventricular conduction throughout the uninvolved or "normal" ventricle remains relatively undisturbed by the bundle branch block and that in the "abnormal" ventricle the excitatory process is delayed and its spread aberrant. Moreover, the order of excitation of part of the septum is also subject to change. With normal conduction it is probable, as Lewis[8] believed, that activation of the septum proceeds from both sides more or less simultaneously. If, however, bundle branch block occurs, there is little reason to doubt that activation of the entire septum as well as that of the "abnormal" ventricle proceeds from the undisturbed side. When intraventricular conduction fluctuates between a presumably normal type and bundle branch block, the electrocardiographic changes that occur are presumably due to intermittent existence of the previously mentioned disturbance of mechanism.

When intraventricular conduction is normal, the QRS complex may be regarded as reflecting the summation of right and left ventricular electromotive forces during that period (in other words, summation of the dextrocardiogram

and levocardiogram), although because of slight grades of asynchronism of activation, its beginning and ending may result from part of the activation of either one or the other ventricle alone. However, when bundle branch block develops, it may be assumed on the basis of experimental studies in dogs by Lewis[5] that early deflections in the QRS complex in human beings (perhaps those recorded during the first 0.04 to 0.06 second) reflect the electrical activity which occurs during such a period in the "normal" ventricle, the septum, and, perhaps, some of the myocardium near the septum, ordinarily activated via the other ventricle, whereas the late deflections added to the QRS complex reflect aberrant spread of the excitatory process in the "abnormal" ventricle.

For these reasons, analysis of the similarities and differences in the deflections of ventricular complexes in patients who at one time exhibit normal intraventricular conduction and at another time bundle branch block should be a method of obtaining information regarding the contribution of one ventricle to electrocardiographic leads that does not have to depend on assumptions of uncertain value. At least one might hope to discover whether current views regarding the mechanism of bundle branch block can be reconciled with those of electrical axis and whether Lewis' ideas regarding the dextrocardiogram and levocardiogram have a useful application to human bundle branch block, even though he may have been in error as to the order of excitation. Accordingly we report here certain findings in the electrocardiograms of five patients who showed periods of alternation between presumably normal intraventricular conduction and right bundle branch block (Figs. 1 to 5); and for purposes of comparison, certain electrocardiographic leads of patients exhibiting transient left bundle branch block are included. In one (Fig. 6) the transition from left bundle branch block to normal type intraventricular conduction and back again to left bundle branch block, as recorded in Lead I, is shown. In the second (Fig. 7) the transition from left bundle branch block to normal intraventricular conduction in Lead III is shown. In the third, obtained from a patient with marked left ventricular enlargement (Fig. 8), a comparison of ventricular complexes obtained with an exploring electrode placed over the right side of the precordium during normal type intraventricular conduction and during left bundle branch block is illustrated. In the fourth (Fig. 9) two isolated beats that exhibit recovery from left bundle branch block are shown in a CR_1 lead.

Criteria for Selection of Cases Showing Right Bundle Branch Block.—In selecting the cases of right bundle branch block for this presentation an attempt was made to avoid the possibility that differences in ventricular complexes which developed in association with bundle branch block were due to any other ventricular change than the bundle branch block itself. This possibility is avoided in Case 1 (Fig. 1) because each lead shows both normal and bundle branch block types of complexes. It is likewise avoided in the limb leads of Case 2 (Fig. 2, *B*) for the same reason. Moreover, in Case 2 the electrocardiogram preceding the episode of bundle branch block (Fig. 2, *A*) was found to be essentially the same as one obtained after the disappearance of bundle branch block. In Cases 3 and 4 (Figs. 3 and 4, respectively) the transition between normal

type intraventricular conduction and right bundle branch block was not recorded, but in each instance the ventricular complexes obtained before and after the episodes of bundle branch block shown were essentially the same. The bundle branch block in Case 5 occurred during an attack of acute pericarditis. The QRS complexes before and after bundle branch block were essentially the same but there were changes in the T waves.

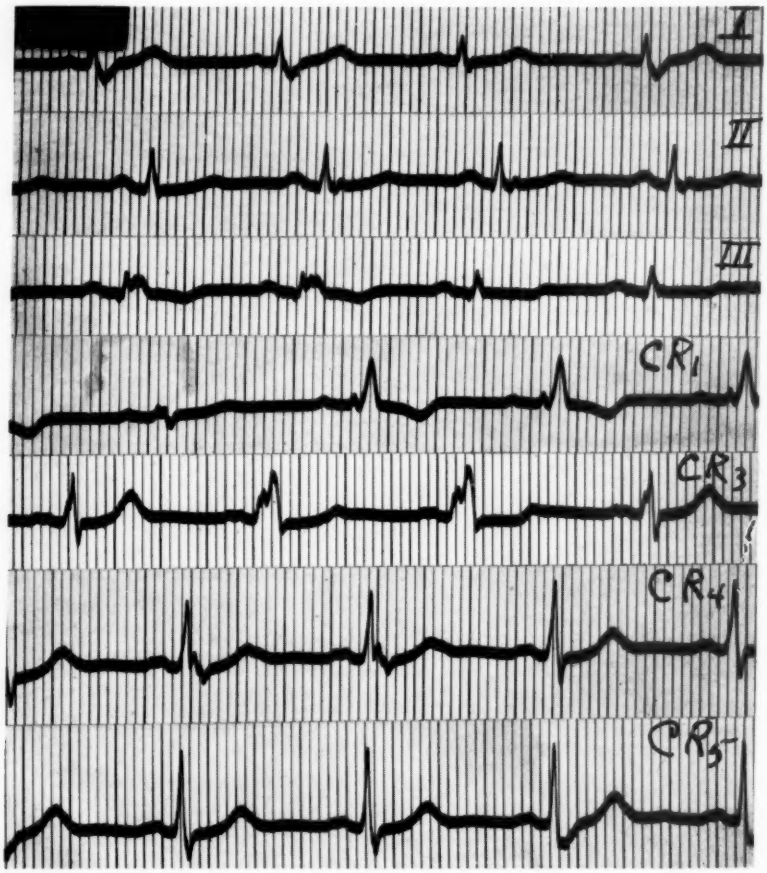

Fig. 1.—Case 1. Beats exhibiting normal type intraventricular conduction and right bundle branch block in all leads. In beats of the normal type the ascending limb of the intrinsic-like deflection in CR_3 is relatively late, being preceded by an upward deflection less steep in slope. The latter corresponds in time to the upward limb of the intrinsic-like deflection found in Leads CR_4 and CR_5. The fact that even in Leads CR_1 and CR_3 the first 0.03 second of the QRS complex is not altered by right bundle branch block indicates that this part of the complex is left ventricular in origin in both types of beat. In limb leads and in Leads CR_4 and CR_5, in contrast to CR_1 and CR_3, the main deflections of the QRS complex and the T waves are found to change only slightly as a result of right bundle branch block.

Clinical Data in Cases of Right Bundle Branch Block.—None of the five patients was hypertensive, showed any signs of valvular disease, or was found to have enlargement of either ventricle by x-ray examination.

Case 1, a man 58 years of age, discovered in a so-called health survey, was working full time, regarded himself as healthy, and had no symptoms nor history of heart disease. Case 2, a physician 65 years of age, had been disabled for several years by the anginal syndrome. About a year after the episode of bundle branch block was recorded he began to exhibit electrocardiographic changes pointing to damage of the left ventricle. Case 3, a university professor 64 years of age, had previously suffered from A-V heart block and mild Adams-

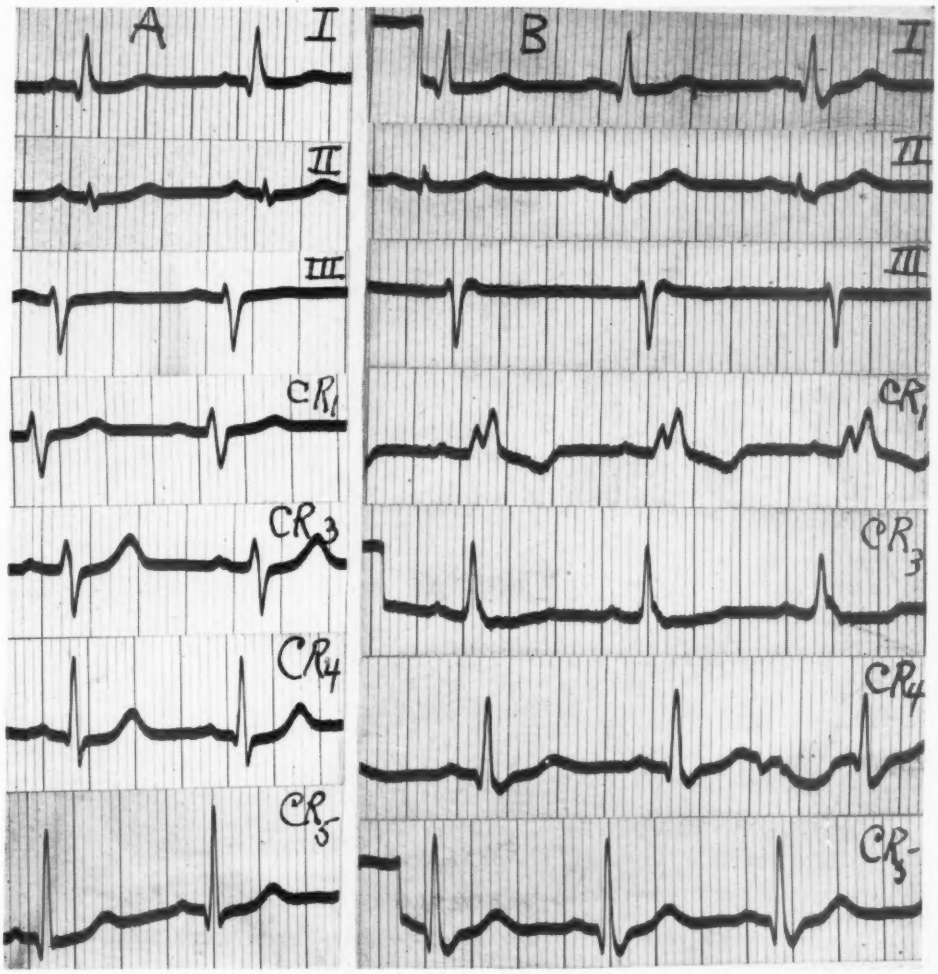

Fig. 2.—Case 2. *A* was obtained prior to the episode of transient intermittent right bundle branch block shown in *B*. In the latter, both normal type beats and right bundle branch block are found side by side in limb leads, although all beats in precordial leads are of the bundle branch block type. The disturbance of mechanism in this case is slightly different from that in Case 1 in that in Leads CR_1 and CR_3 differences in ventricular complexes of the two types of beats exist from the very beginning of the QRS complex. The ascending limbs of the first deflection of CR_1 look somewhat alike, but the slope is less steep in bundle branch block. As in Case 1, the main deflections of the QRS complex and the direction and amplitude of T waves in limb leads and precordial leads CR_4 and CR_5 are little influenced by bundle branch block.

Stokes seizures. Case 4, a business executive 59 years of age, had suffered an attack of acute coronary occlusion with posterior myocardial infarction several years prior to the occurrence of bundle branch block but had made a good recovery. Case 5 (Fig. 5), a woman 61 years of age, developed what appeared to be acute pericarditis following a surgical operation. During this period one electrocardiogram, made when the cardiac rate was quite rapid, showed right

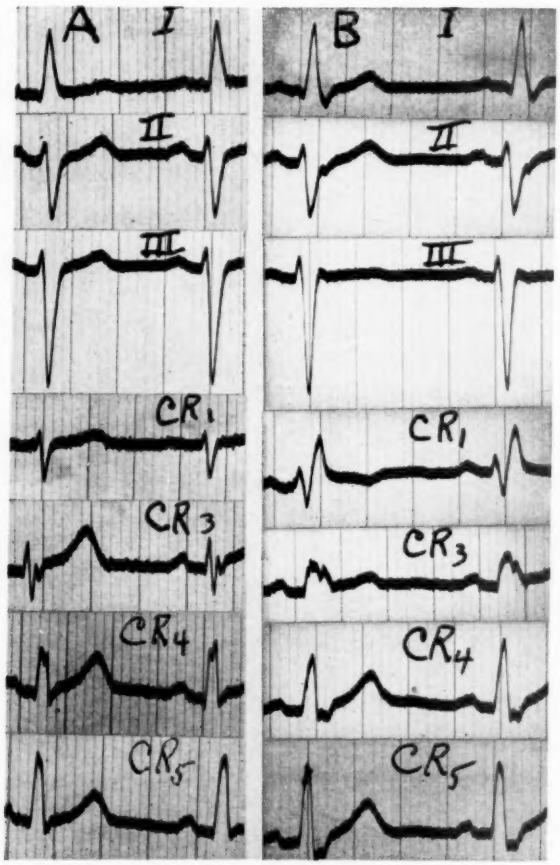

Fig. 3.—Case 3. *A* was obtained prior to *B*, which exhibits right bundle branch block. Following the episode of bundle branch block, another electrocardiogram was obtained similar to *A*. As in Case 2, Leads CR_1 and CR_3 show changes in the QRS complex from its beginning. The main deflections of the QRS complex and T wave of limb leads are little changed by right bundle branch block. There are minor differences in the QRS complexes of Leads CR_4 and CR_5.

bundle branch block. This finding raised a rather pointed question as to whether the pericarditis might not be associated with myocardial infarction, a possibility that could not be ruled out completely. It seemed proper to include this case, however, because the QRS complexes obtained in tracings before and after the bundle branch block were essentially the same.

Changes in QRS Complexes Associated With Right Bundle Branch Block.—One of the most striking phenomena observed in the five cases of right bundle branch block was the lack of pronounced change in the main deflections of the QRS complexes in limb leads as a result of bundle branch block. In Cases 1,

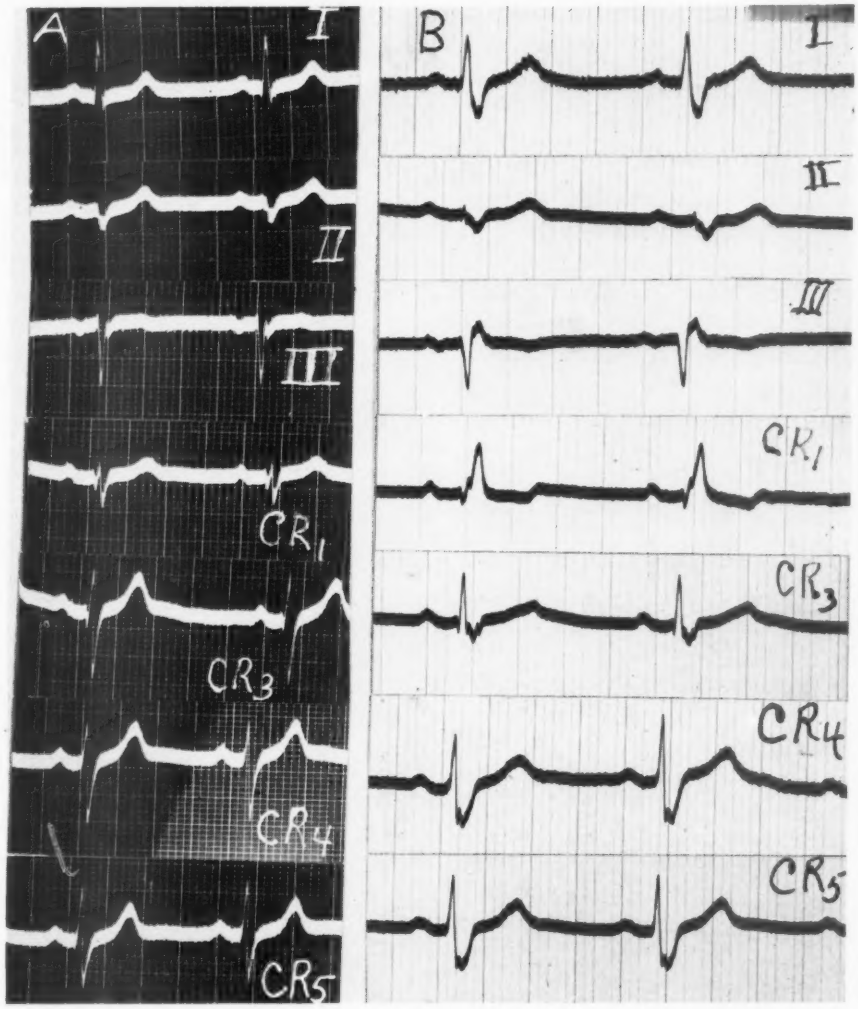

Fig. 4.—Case 4. *A*, made with a portable machine, was obtained prior to the episode of right bundle branch block shown in *B*. Allowance must be made for the differences in speed of photographic paper as well as the faster response of the beam of the machine used to obtain *B*. Very slight changes in the early part of the QRS complex in Leads II and III occur during bundle branch block. The T wave changes, although minor except in CR_1 and CR_3, are great enough to cause change of direction in Lead III.

2, and 3 the limb leads were practically identical during normal conduction and during periods of bundle branch block. In Case 4 (Fig. 4), a small upward deflection was observed early in the QRS complex in Lead II during bundle

branch block that was not recorded when the intraventricular conduction time was within normal limits. In Lead III, however, there was a correspondingly small initial upward deflection in the "normal" tracing which practically dis-

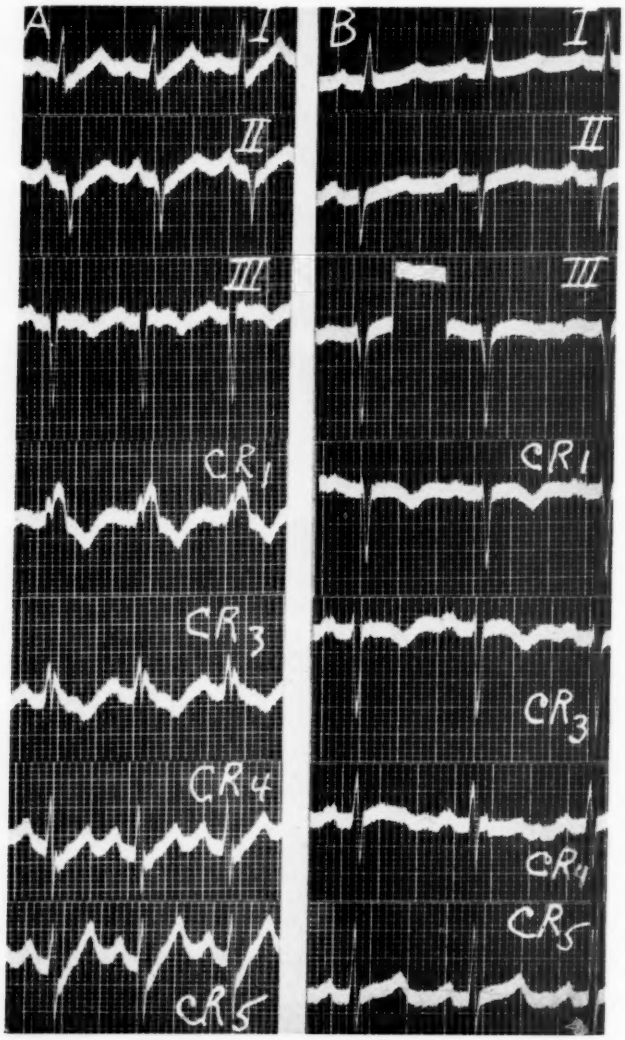

Fig. 5.—Case 5. *A* was made during a transient period of right bundle branch block and *B*, two days later. Although the main deflections of the QRS complex are much the same in limb leads and precordial Leads CR_4 and CR_5, there are slight differences in the initial part in limb leads. The differences are marked in CR_1 and CR_3. The T-wave changes may be attributed in part to the active pericarditis present when both tracings were made.

appeared during bundle branch block. In Case 5 (Fig. 5) there were also minor differences in the beginning of the QRS complex in association with bundle branch block. The most conspicuous difference was the loss of a very small initial

upward deflection in Lead II and the disappearance of slight slurring in the beginning part of the downward deflection in Lead III. In all cases the broad terminal deflection developed and prolonged the duration of the QRS to at least 0.12 second, as is characteristic of right bundle branch block. This deflection doubtless reflects the delayed aberrant excitation of the right ventricle.

In comparisons of patterns of precordial leads made at different times, one must allow for the possibility that the relationship of position of exploring electrode and cardiac surface may not be identical. In spite of this limitation, the findings in these five cases permit certain definite statements. Thus, in leads made with the exploring electrode placed on the right side of the precordium, such as in Lead CR_1, radical changes develop in association with bundle branch block. In some instances, however, the pattern of the QRS complex is not altered by bundle branch block during the first 0.02 to 0.03 second (Figs. 1 and 4). In others it differs from the very beginning (Fig. 5). In Lead CR_3 the similarity in the beginning of the QRS complexes exists in the same cases in which there is a similarity in CR_1. The main deflections of the QRS complexes recorded with the exploring electrode placed over the left side of the precordium, such as in Leads CR_4 and CR_5, showed remarkably little change as a result of right bundle branch block, although minor differences were observed in Cases 3, 4, and 5 (Figs. 3, 4, and 5).

In all cases the broad terminal deflection during right bundle branch block was relatively large, more or less rounded, and upwardly directed in leads made with the exploring electrode placed over the right side of the precordium. The deflection was much smaller and downwardly directed in leads made with the exploring electrode placed over the left side of the precordium.

Changes in the T Waves Associated With Right Bundle Branch Block.—In the comparison of T waves during normal type intraventricular conduction and right bundle branch block, Case 5 is excluded for reasons stated previously. In the other cases, changes in the amplitude of T waves in limb leads occurred but most of them were minor. Thus, in Lead I of Cases 1, 2, and 3, the T waves were slightly larger during bundle branch block, and in Case 4 they were about the same size. In Lead II changes were very slight. In Case 3 the T waves were definitely smaller in Lead III during bundle branch block, and in Case 4 they changed from practically isoelectric to slightly inverted. The most marked changes in T waves, as well as in QRS complexes, were noted in leads made with the exploring electrode placed over the right side of the precordium. Thus, in Cases 1, 2, 3, and 4 the T wave changed from upright to inverted when right bundle branch block occurred. In the CR_3 leads the T waves also showed marked changes. However, in CR_4 and CR_5 leads the T wave changes were slight and in no instance was the direction changed. In three cases the amplitude of the T waves was slightly smaller and in one case slightly larger in CR_4 leads during bundle branch block. However, in CR_5 leads the T wave was slightly smaller in one case and larger in three cases during right bundle branch block.

Changes in the Ventricular Complexes in Association With Left Bundle Branch Block.—It is obvious from inspection of Figs. 6, 7, and 8 that the patterns of

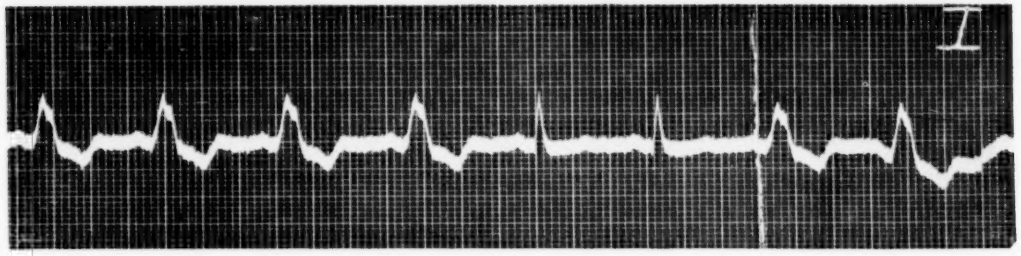

Fig. 6.—Interruption of left bundle branch block by two normal type beats in Lead I. No resemblance was noted between the ventricular complexes in the two types of beats.

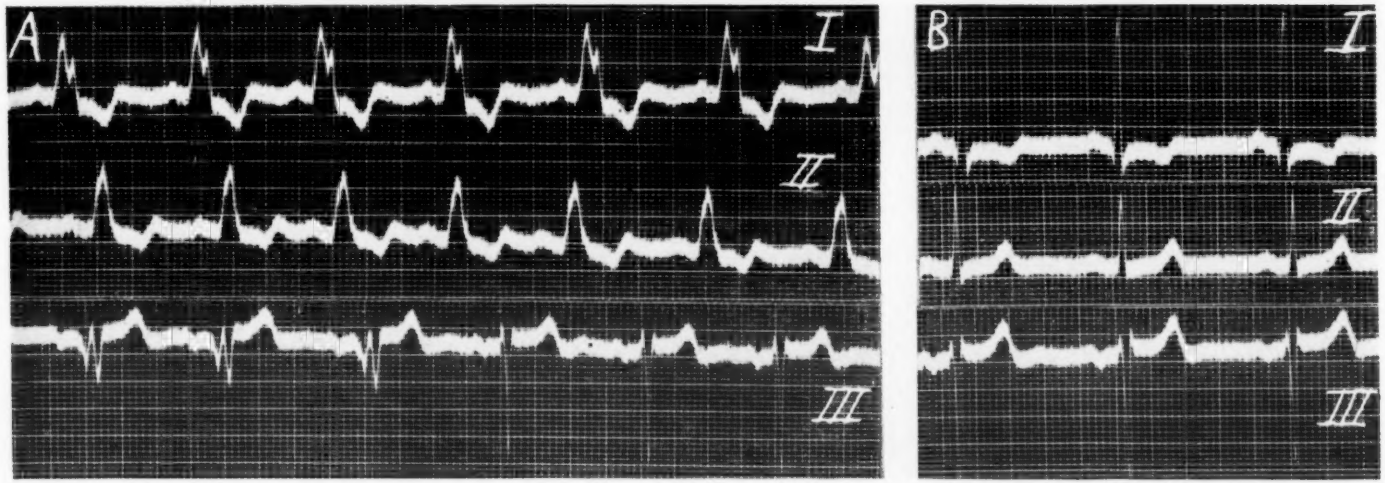

Fig. 7.—*A* shows change from left bundle branch block to beats with normal intraventricular conduction time in Lead III. *B*, obtained later, shows a marked grade of so-called left axis deviation. No resemblance was noted in the QRS complexes of the two types of beats in any of the three leads. The resemblance of T waves in Lead III is probably a coincidence. The differences in Lead II are quite marked.

ventricular complexes are radically changed in Leads I and III when left bundle branch block develops. Thus, the QRS complex in these leads shows no resemblance whatever to the pattern found during normal type intraventricular conduction.* In fact, the only resemblance of QRS complexes we have ever been able to discover is found in leads made with the exploring electrode placed over the right side of the precordium. In such leads there is always a sharp downwardly directed movement early in the QRS complex both during normal type intraventricular conduction and left bundle branch block. In both conditions this downward movement is usually, but not always, preceded by an upward movement so that a peak is formed above the isoelectric line. The upward movement tends to be smaller in bundle branch block (Figs. 8 and 9).

Usually there is marked change in the T wave with the development of left bundle branch block, as in Fig. 6. Fig. 7 is exceptional in that the T wave in Lead III shows little change following reversion to normal type intraventricular conduction. This was probably a coincidence because the T waves in Leads I and II were markedly changed by bundle branch block.

DISCUSSION

In the five cases of transient right bundle branch block presented, it is clear that, if current views regarding the aberrant course of the excitatory process in the two main types of bundle branch block are correct, the main deflections of the QRS complex in limb leads were contributed almost entirely by the left ventricle and the part of the septum activated via the left ventricle. The right ventricle and the part of the septum ordinarily activated by it appear to have had very little influence in the formation of these deflections. Moreover, the influence of the right ventricle on the characteristics of the T waves in limb leads also appears to have been slight. The "bicardiogram" or actual electrocardiogram in limb leads was formed almost entirely by the "levocardiogram." This statement applies equally to our cases with "left axis deviation" and "normal electrical axis." It should be emphasized that these were cases without evidence of right ventricular enlargement or hypertrophy. Had we been dealing with such cases, much greater changes in the main deflections of the QRS complex and, perhaps also the T waves, might have been expected as a result of right bundle branch block. One of Wilson's[6] patients having mitral stenosis, showed more change than any of our patients.

The radical change in the entire ventricular complex in limb leads caused by left bundle branch block adds further support to the view that the left ventricle was the structure in that group of cases almost entirely responsible for the pattern found when intraventricular conduction was of the normal type. An objection to the thesis that the right ventricle contributed relatively little to limb leads in these cases may be raised on the ground that differences of potential of considerable magnitude developed early in the QRS complexes during left

*The statement has sometimes been made that there is a resemblance between limb lead ventricular patterns of certain cases with marked left ventricular enlargement and those of left bundle branch block. Examination of the actual deflections, however, shows that what similarity exists is merely a coincidence (Fig. 8).

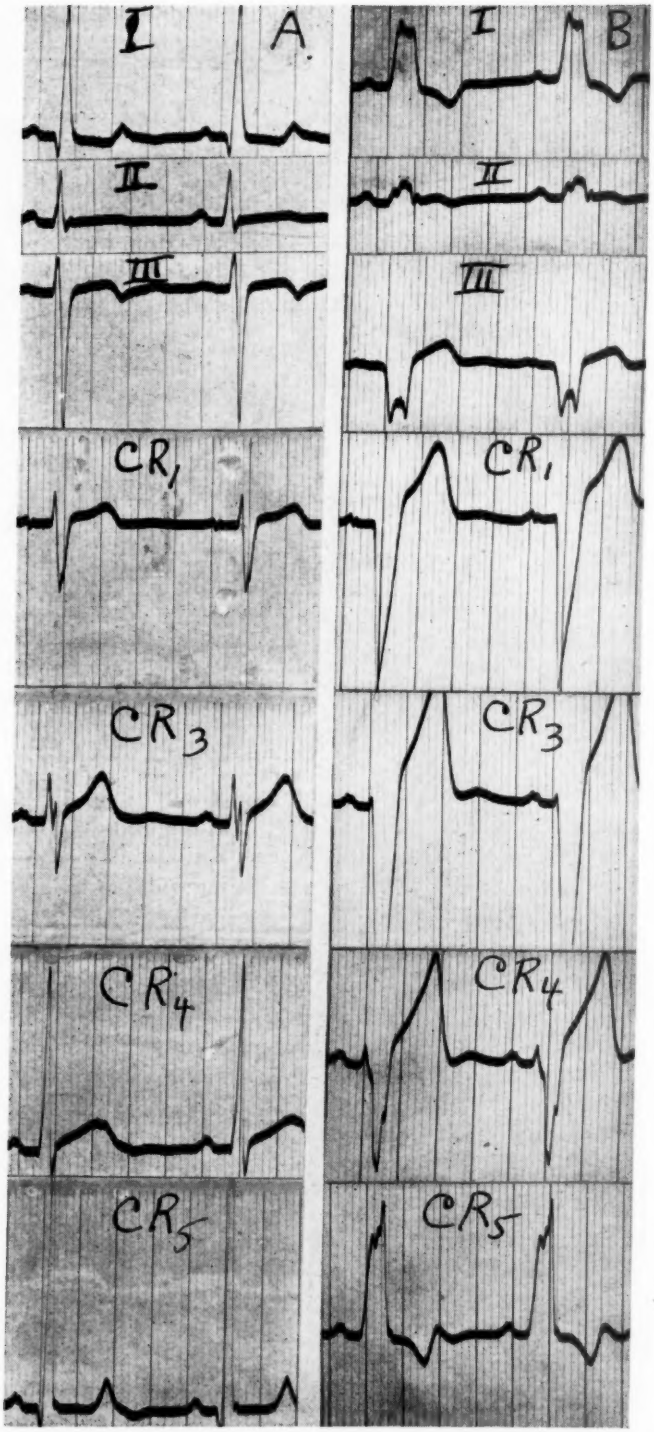

Fig. 8.—The patient from whom these electrocardiograms were obtained had rheumatic type of aortic insufficiency with great enlargement of the left ventricle. In the limb leads and the precordial leads CR_4 and CR_5 no resemblance between beats exhibiting the two types of intraventricular conduction could be observed. In the precordial leads CR_1 and CR_3 during bundle branch block a large early deflection of the QRS complex is noted which may represent the right ventricular component of the early deflection recorded in the QRS complex of CR_1 in *A*. The sharp downward deflection of the QRS complex, beginning 0.06 second after the beginning of the complex in Lead CR_4, *B*, probably reflects excitation of the part of the surface of the left ventricle adjacent to the septum.

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bundle branch block, presumably before activation of the left ventricle took place. The explanation for this must await more detailed studies of the course of the excitatory process in left bundle branch block. However, during the early part of the QRS complex the excitatory process, in addition to activating the

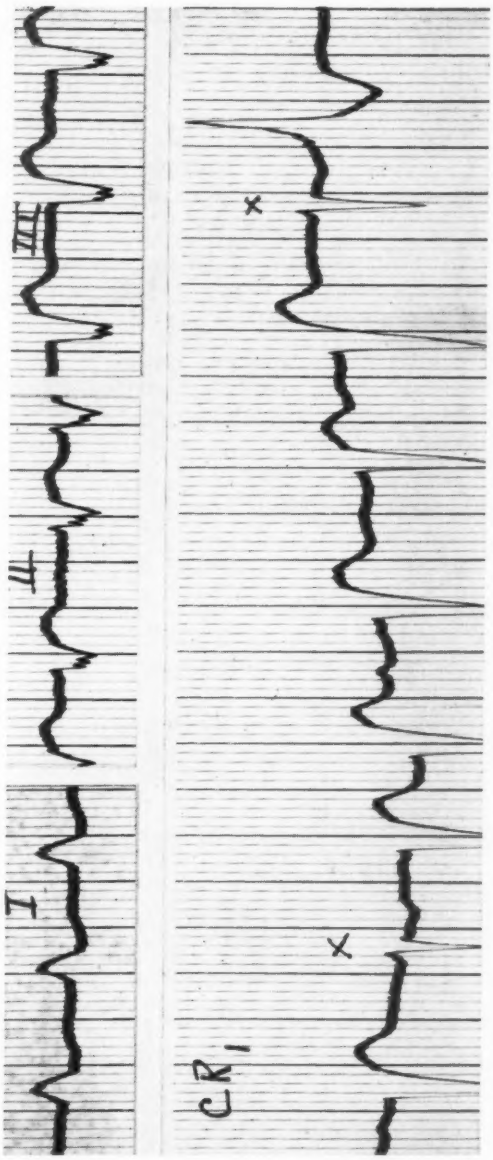

Fig. 9.—Auricular fibrillation and left bundle branch block. The second and eighth beats in the precordial lead CR_1 marked *X* show temporary recovery from left bundle branch block. Note the resemblances of an early deflection of the QRS complexes in both types of beats. The differences are that in the normal type beats it falls a little later, the upward limb seems slightly larger, and the descent is less in amplitude.

right ventricle, also must begin its aberrant course throughout the left side of the septum and it may also reach contiguous parts of the left ventricle.*

Lewis[5] noted in experimental canine bundle branch block that direct leads made from the ventricular surfaces showed no delay in the arrival of the intrinsic deflection at the exterior surface of the contralateral ventricle, whereas in the case of the homolateral ventricle, the conduction tracts of which had been transected, the arrival of the intrinsic deflection was markedly delayed (up to 0.035 to 0.04 second). Wilson and co-workers[6] found that the intrinsic-like deflections of semidirect leads exhibited the same behavior. He also observed that a precordial lead shows a marked resemblance to that of the underlying semidirect lead. Thus the chain of evidence in the dog demonstrating that the pattern of a precordial lead resembles the pattern of a lead made with an exploring electrode placed on the directly underlying surface of the ventricular myocardium was completed. However, among the qualitative differences in pattern between a precordial lead in bundle branch block and a direct lead from the underlying ventricular surface is the fact that in precordial leads made with the exploring electrode placed over the side of bundle branch block, the intrinsic-like deflection tends to be lost.† On the other hand, it is well preserved in precordial leads made with the exploring electrode placed over the side of the "normal" ventricle. The reasons for this difference need not be elaborated here beyond stating that the most important reason probably is that in the normal ventricle a comparatively large area of surface is excited at practically the same time with summation of electrical effects, whereas in bundle branch block excitation of an area the same size is a much longer drawn-out process, with less summation, somewhat similar to that of auricular excitation. In any event, it is the behavior of the right- and left-sided intrinsic-like deflections in precordial leads that furnishes the key to the recognition of the side of the lesion in bundle branch block or in even lesser grades of intraventricular conduction defect. If, however, the right-sided intrinsic-like deflection is a little late when intraventricular conduction is of the normal type, as in Case 4 (Fig. 4), the fraction of the QRS complex that precedes it does not necessarily change when bundle branch block develops.‡

*The sharp downward deflection, usually beginning about 0.04 to 0.06 second after the beginning of the QRS complex, which is recorded in almost all cases of left bundle branch block (but only in leads made with the exploring electrode placed on a localized area, usually a little toward the left side of the precordium), probably reflects the arrival of the excitatory process at a part of the anterior surface near the septum ordinarily activated via the left ventricle (Fig. 8, *B*, Lead CR_4).

†The terms right- and left-sided intrinsic-like deflection, as used in this paper in connection with precordial leads, refer to the combinations of sharp upward and downward movements, each forming a peak in the QRS complex of certain leads. The upward and downward movements are regarded as a unit irrespective of their relation to the base line. The left-sided intrinsic-like deflection, when it is not abolished or modified by disease or a conduction defect involving the anterior wall of the left ventricle, is easily recognized. The right-sided deflection, in which the upward and downward movements, especially the former, are usually much less in amplitude, may be obscured by "unexplained deflections" introduced via the reference electrode unless it is placed on the right arm or preferably over the spine of the right scapula.

‡Minor grades of intraventricular conduction defect constitute an almost unexplored field. There can be little doubt that duration of the QRS complex as the sole criterion is unsatisfactory even though the attempt is made to develop standards that take into account the size of ventricles. Thus, the right-sided intrinsic-like deflection, which probably signals the passage of the excitatory process through the anterior wall of the right ventricle, usually occurs very early in the QRS complex. However, it can be subject to pronounced delay without actual prolongation of the QRS complex (Fig. 1, Lead CR_3 and unpublished observations). The part of the QRS complex that precedes it is not necessarily derived

In other words, under these circumstances the initial part of the QRS complex may be levocardiogram when intraventricular conduction time is within normal limits. If it is, the development of right bundle branch block extends the period of the unmodified levocardiogram in the electrocardiogram until the delayed aberrant excitatory process begins to activate the right ventricle. The influence of the right ventricle on the QRS complex of precordial leads made from the left side of the precordium as well as limb leads, however, is so negligible that even when the right-sided intrinsic-like deflection occurred at the very beginning of the QRS complex, its disappearance, as a result of bundle branch block, caused, at most, insignificant changes in the early part of the QRS complex of those leads. Thus, in these cases, it was only in leads made with an exploring electrode placed over parts of the precordium near the right ventricle that this structure exerted an important effect on the form of the main deflections of the QRS complex.

The almost constant finding of inverted T waves in CR leads made from the right side of the precordium in right bundle branch block can be attributed, at least in part, to the aberrant course of the excitatory process in the right ventricle and consequent aberrant order of return to the resting phase. The evidence for this is that in each of our cases inversion of the T wave developed only when bundle branch block was present. Moreover, it seemed equally clear that right ventricular electrical activity had only slight influence on the T waves in CR leads recorded from the left side of the precordium, because they were only slightly changed as a result of right bundle branch block, despite the pronounced changes in the T waves in leads made with an exploring electrode placed over the right side of the precordium.

The direction and relative amplitude of the broad terminal deflection of the QRS complex in right bundle branch block in the various precordial leads appear to show the same type of behavior in all cases. First of all, its characteristics indicate that even though normal type excitation of the right ventricle may have little effect on the QRS complex and T wave of certain leads, an abnormal delayed type of excitation can be registered distinctly at the end of the QRS complex of the same leads. This abnormal deflection, like RS-T segment displacement following obstruction of a coronary artery, presumably arises from abnormal electrical activity in a limited part of the heart (in right bundle branch block, the right ventricle) and occurs, at least in part, during a period of time when it is not obscured by deflections caused by activity elsewhere in the heart. Although the mechanisms responsible for these two types of deflections are totally different, their behavior is in some respects analogous. Thus, in both the displacement is upward when the exploring electrode is placed directly over the area of involvement, and it is greater in such leads than in any other. Moreover, in both conditions, when the exploring electrode is placed at a distance

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entirely from the left ventricle but might be derived in part from excitation of some other part of the right ventricle. Under such circumstances, if right bundle branch block developed, the initial part of the QRS complex as well as the intrinsic-like deflection would be modified or would disappear from leads made from the right side of the precordium, depending on the time relations of the right-sided intrinsic-like deflection, the beginning of excitation elsewhere in the right ventricle, and the beginning of excitation of the left ventricle prior to the development of bundle branch block.

from the area of involvement, the displacement is in the opposite direction and the amplitude is less. Thus, it would appear that the principle governing reciprocal relationships of direction of RS-T segment displacement at various parts of cardiac surfaces,[9] which is reflected in body surface leads, also applies, to some extent at least, to the broad terminal deflection of right bundle branch block. It is probable that the opposite directions of the deflection in the terminal portion of the QRS complex in left bundle branch block in leads made from the right and left sides of the precordium furnish a manifestation of the same principle regarding the distribution of potential.

In view of the foregoing findings, the possibility that Wilson's views regarding the classification of bundle branch block are incorrect and that what is now called right bundle branch block is actually left bundle branch block and vice versa should be reconsidered. On the basis of the evidence presented here the proponents of this view would have to maintain that when intraventricular conduction is of the normal type the right ventricle is almost entirely responsible for the pattern of ventricular complexes in limb leads and that the left ventricle, despite the fact that its muscle mass is usually far greater than that of the right ventricle, exerts a negligible influence. Greater trouble would arise in trying to account for the findings in precordial leads. It would be necessary to assume, in view of the positions of the exploring electrode at which the greatest changes occur in bundle branch block, that activation of the left ventricle produces far greater potential variation over the right side of the precordium than over the left, which is much nearer to it, and that the right ventricle produces far greater potential variation over the left side of the precordium than over the right side. Such an assumption would have to ignore the findings in Wilson's studies of semidirect and precordial leads in experimentally produced canine bundle branch block,[6] which indicate that patterns of differences of potential recorded with an exploring electrode on a precordial surface tend to resemble those obtained with the electrode close to the directly underlying part of the ventricular muscle. As a result of such observations, as well as those of Wolferth and Margolies referred to earlier, it has seemed to us that Wilson's views regarding the electrocardiographic criteria that reveal the side of the lesion in bundle branch block are sound. The doubt that has been expressed in the past has been on the basis of limb lead criteria which are admittedly not completely satisfactory in some cases. There has been no effective criticism of the validity of the evidence derived from cardiac surface and precordial leads.

Inasmuch as the changes in electrocardiograms that develop as a result of bundle branch block are not in accord with the hypothesis of electrical axis, irrespective of whether current views regarding bundle branch block are satisfactorily established, the fault must be with the hypothesis of electrical axis. What evidence there is to favor that hypothesis has been fully presented many times and does not require repetition here. It should be said, however, that the evidence to support it, which is obtained from changes in electrocardiograms that result from change in position of the heart or enlargement of one or the other ventricle, begs the question because the hypothesis was constructed to account for such findings. The fact that Lewis, reasoning accurately, could use it to his

complete satisfaction to account for the deflections of QRS complexes in human bundle branch block, even though he was mistaken as to the side of the lesion, illustrates the nature of what can happen if this pitfall of logic is not avoided.

The results of the present study considered alone do not rule out application of the concept of electrical axis to electrocardiograms, although they necessitate certain modifications of present ideas. One may still assume, if he wishes, that an axis rotates. He is forced by the evidence to concede that rotation in the right ventricle, provided that chamber is not enlarged, exerts little influence on the patterns of the main deflections of the QRS complexes in limb leads. If, then, he assumes that the QRS complexes of limb leads are formed mainly by rotation of the axis in the left ventricle, he still has before himself the problems of explaining (1) the nature of the coincidence accounting for the fact that a pattern of differences of potential, recorded by the method of balanced potentials with an exploring electrode placed near the left border of the precordium, can be preserved, even including the intrinsic-like deflection, when the exploring electrode is moved to the left arm and (2) why (a) infarction in one part of the left ventricle causes change in rotation of the axis in one direction, (b) infarction in a second position causes change in rotation in the opposite direction, and (c) infarction in a third position causes no change in rotation. For such reasons we retain an interest only in the historic aspects of the hypothesis of electrical axis. It seems to be one of the numerous dubious results of attempting to apply to the body the laws that account for electrical behavior in models. It has not as yet been established that a complex aggregate of biologic structures like that of the human body behaves electrically like the physicist's models and there is some evidence against that view.[10-12]

The observations made here on bundle branch block support the concept that electrocardiographic leads can be analyzed from the point of view of summation of right and left ventricular effects (in other words, dextrocardiogram and levocardiogram) if one chooses to use those terms. However, the views of Lewis, based on reasoning that assumed the validity of the Einthoven equilateral triangle hypothesis, are not supported. The evidence is more in accord with the view that there are favored avenues of conduction between the heart and the extremities.[12] As far as precordial leads are concerned, the dextrocardiogram seems to play an important but not exclusive role in shaping leads made with an exploring electrode placed over the right side of the precordium, whereas the levocardiogram is predominant in leads made with an exploring electrode placed over the left side of the precordium.

SUMMARY

1. Five cases of transient right bundle branch block are reported which showed that the main deflections of the QRS complex in limb leads were very slightly altered as a result of right bundle branch block, although all cases showed the broad terminal deflection characteristic of that condition. The T waves of limb leads likewise showed only slight alterations during bundle branch block. Precordial leads made with the exploring electrode placed over the right side

of the precordium showed marked changes in both QRS complexes and T waves during bundle branch block. In some cases, however, there was no change in the earliest part of the QRS complex. Leads made with the exploring electrode placed over the left side of the precordium showed little change except for the broad terminal deflection of the QRS complex.

2. The development of left bundle branch block produced radical changes in the ventricular complexes of the same leads that were little changed by right bundle branch block. However, in the leads most radically changed by right bundle branch block (namely, those made with an exploring electrode placed over the right side of the precordium) an early deflection in the QRS complex was preserved, although somewhat modified in certain of its characteristics.

3. The changes in the ventricular complex that occur in bundle branch block indicate, provided current views as to the mechanism of bundle branch block are sound and also provided the right ventricle is not enlarged, that (1) the left ventricle and the part of the septum normally activated via the left ventricle are the source of electrical activity mainly responsible for the main deflections of the QRS complexes and also the T waves of limb leads, as well as leads made with the exploring electrode placed over the left side of the precordium when intraventricular conduction is of the normal type, and (2) the right ventricle is mainly, although not completely, responsible for differences of potential in leads made with the exploring electrode placed over the right side of the precordium. These findings are not in accord with views widely held regarding the parts played by the two ventricles in the hypothesis of electrical axis. They indicate that, except in leads made with an electrode placed near the right ventricle, the levocardiogram tends to contribute far more to the electrocardiogram than the dextrocardiogram. This, considered in connection with evidence that (1) certain parts of the left ventricle are electrocardiographically silent as far as "axis" is concerned and (2) by certain methods of pairing electrodes the pattern of differences of potential obtained with an exploring electrode placed just to the left of the precordium closely resembles that obtained by moving the exploring electrode to the left arm, appears to expose the hypothesis of electrical axis to the charge of having been a hindrance to progress in understanding the nature of the mechanisms concerned in the formation of electrocardiograms.

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TOBACCO ANGINA

An Electrocardiographic Study

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SINCE Huchard used the term tobacco angina in 1899,[1] there has been much discussion of the relation which it suggests, but few definitive studies of this relation have been published. A review of the literature reveals only two case reports which present objective evidence of myocardial ischemia during anginal seizures induced by smoking.[2] It is the purpose of this paper to discuss some of the cardiovascular effects of tobacco and some observations in sixteen patients with angina pectoris in whom electrocardiograms were taken immediately after the patient had smoked two cigarettes.

Numerous observers have expressed the opinion that a close temporal relation between the use of tobacco and the onset of cardiac pain is exceedingly rare.[3-5] The majority of articles dealing with tobacco angina present little or no evidence that smoking is a cause of anginal seizures.[1,5-12]

Investigation of the effects of tobacco in man have been concerned mainly with the response of the peripheral vascular system. It is generally agreed that smoking usually induces arteriolar constriction, accompanied by lowering of the temperature of the skin and elevation of the blood pressure, pulse rate,[13-21] and blood sugar.[22] There are, however, various opinions with respect to the particular products of smoking responsible for these phenomena and the mechanisms through which they are effected. The question of an allergic response to tobacco smoke in certain cardiovascular diseases has been raised, but the evidence bearing upon it is inconclusive.[15,16,23-25]

There are many observations indicating that nicotine alone is capable of producing many of the reactions caused by smoking,[16,19,20,26-28] but some investigators believe that the same cardiovascular responses are induced by smoking material that does not contain this drug.[20] The initial effect of nicotine is to stimulate, but its subsequent and more prolonged action is to depress the parasympathetic and sympathetic ganglia, central nervous system cells, and skeletal

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muscles. The results which follow its administration are, therefore, complex and unpredictable; they represent a varying combination of many different effects.[28] The magnitude of the response to nicotine varies from one time to another.[15,19] Studies of the effects of this drug and of tobacco smoke on the coronary blood flow have yielded conflicting results.[29-31] The complex action of nicotine and the many extrinsic as well as intrinsic factors influencing coronary flow suggests that this approach to the problem of its effects in man is of little value. Furthermore, as has been pointed out,[2] it cannot be assumed that diseased and normal coronary arteries will invariably react in the same way to a given stimulus. Physiologic and anatomic abnormalities are, so it would seem, likely to be found in company.

Statistical studies indicate that coronary disease develops before the seventh decade of life significantly more often in smokers than in nonsmokers[32,33] and that the life span of the former is shorter.[34] Pathologic studies comparing the coronary arteries of these two groups have not been reported. Experiments on animals have brought forth no evidence that tobacco smoke or nicotine produces structural changes in these arteries.[35] After coronary ligation in dogs, there is a pronounced increase in the sensitivity to tobacco smoke and nicotine, as evidenced by cardiac arrhythmias.[36] It has not been proved that smoking has an effect on the coronary vessels comparable to its unquestioned deleterious effect on the peripheral arteries in certain diseases.[37,38]

The most consistent effect of tobacco smoking upon the electrocardiogram of normal subjects is an acceleration of the heart rate with accompanying physiologic changes in the T wave,[19,20,39-42] which involve a reduction in the size; less often, inversion of this deflection. Although it is known that in some persons smoking may raise the pulse rate without altering the blood pressure or cardiac output,[43] these electrocardiographic changes have usually been attributed to increased cardiac work.[19,40,41] These changes have been referred to in a manner which suggests the inference that they are due to a direct effect of smoking upon the myocardium.[4,28,41] However, it has been clearly demonstrated in the case of normal subjects and in the case of the majority of patients with heart disease that the changes in the T wave induced by smoking and those induced by other agents which elevate the resting heart rate to a similar level are alike in kind and magnitude.[44,45] These electrocardiographic phenomena represent a physiologic response which has been studied both from the theoretical and from the empirical standpoint.[45,46] The administration of drugs that slow the heart is accompanied by an increase in the height of the T wave and the administration of those drugs that accelerate the rate is accompanied by a decrease in the height of the T waves. The latter effect occurs even when the drug given belongs to the parasympathomimetic group.[44,47]

There is a sharp difference of opinion concerning the mechanism through which smoking precipitates paroxysms of angina pectoris. One group of observers[3,5,6,41,48] attributes all such paroxysms to increased cardiac work resulting from an elevation of the blood pressure and the heart rate and ignores or discounts the possibility of coronary constriction. Others[1,2] believe that in some instances the occurrence of coronary spasm can hardly be doubted. Moreover,

from the time of Allbutt[6] to the present time[49] the idea has persisted that there is a fundamental difference in the pathologic background between tobacco angina and true angina pectoris.

The most recent paper on the relation of smoking to angina pectoris is that of Pickering and Sanderson.[5] In a detailed study of one patient, they found that smoking was attended by the occurrence of anginal pain only under certain circumstances; that is, only when the subject smoked immediately following the subsidence of a paroxysm precipitated by exercise and while a significant elevation of the pulse rate and blood pressure were still present. From these data, which did not include electrocardiographic tracings, the writers concluded that their "paper . . . has rendered redundant the hypothesis that constriction of the coronary arteries by tobacco is the cause of anginal attacks precipitated by smoking." This conclusion does not harmonize with numerous reports since the time of Heberden[50] to the effect that seizures were witnessed in which "the pulse was not quickened"[50-52] or in which no significant alteration in pulse or blood pressure occurred.[2,53,54]

In 1939, Wilson and Johnston[2] studied two patients with angina pectoris in whom paroxysms and transient electrocardiographic changes, similar in magnitude and in kind to those produced by myocardial infarction, were induced by having the patients smoke. In one of these (Case 5) no alteration in the pulse rate or blood pressure accompanied the electrocardiographic changes. These observers suggested that, in certain instances, changes in the caliber of the coronary arteries or arterioles rather than increased cardiac work must be assumed to explain the attendant myocardial ischemia. Levy and collaborators[55] and Master and co-workers[56] have shown that, in patients with coronary insufficiency, painless myocardial ischemia induced by anoxemia or exercise can be demonstrated electrocardiographically. It is, therefore, possible that if Pickering and Sanderson had made electrocardiographic observations while their patient was smoking, they might have found evidence of myocardial ischemia without pain.

There is considerable evidence indicating that the coronary circulation is regulated by direct vasomotor control as well as by purely mechanical factors.[57-59] It is the opinion of most investigators who have carried out experimental studies of coronary flow in animals that it is diminished by vagal and increased by sympathetic stimulation. The observations of Manning, Hall, and Banting,[60] that vagal stimulation in the intact dog uniformly produces areas of myocardial necrosis, which are most extensive after the prior administration of physostigmine and do not occur when atropine has been given, suggests that coronary spasm may be important in the production of myocardial ischemia. These experiments support the clinical observations of Gilbert,[61] who found that in some cases of angina pectoris the administration of atropine definitely increases the coronary reserve as estimated by the Levy anoxemia procedure. The possibility that smoking may cause coronary constriction by stimulation of the vagi is suggested by Hobbs (quoted by Gilbert),[61] who, in two patients with tobacco angina, demonstrated that atropine given prior to smoking prevented the occurrence of electrocardiographic changes of the type described by Wilson and Johnston.[2]

Moreover, Leary's suggestion,[62] that coronary spasm in the absence of obvious coronary disease may sometimes be responsible for sudden death, emphasizes the importance of more adequate knowledge concerning reflex constriction of the arteries of the heart and the effect of tobacco upon this reaction.

MATERIAL

This report is based on observations in sixteen patients with coronary disease in whom the effect of smoking upon the electrocardiogram was investigated. In no instance did the clinical history indicate a relation between the use of tobacco and anginal symptoms. All of the patients had smoked for a long time, but the majority should probably be considered moderate rather than heavy smokers; some did not "inhale." The series includes substantially all patients with symptoms of the kind indicated who were seen in the electrocardiographic laboratory of the University of Virginia Hospital between September, 1943, and October, 1944, and who presented themselves during a period when time to carry out the required special tests was available. This group is composed of two women and fourteen men ranging in age from 38 to 69 years. The diagnosis of coronary disease was made on the basis of one or more of the following criteria: a history typical of angina pectoris; abnormal electrocardiographc findings at rest; or abnormal electrocardiographic changes precipitated by exercise (Master "two-step"), and anoxemia (Levy), or smoking. In two instances a diagnosis of recent anterior myocardial infarction was made on the basis of diagnostic changes in the precordial electrocardiogram.

METHOD

The tests were performed under uniform conditions. After the patient had rested in the recumbent posture for a time sufficient to give a basal heart rate, a control electrocardiogram consisting of the standard and unipolar limb leads was taken. Immediately thereafter the patient smoked two cigarettes of the brand to which he was accustomed. A second electrocardiogram was taken about ten minutes later when he had finished smoking or sooner if he experienced discomfort in the chest. This test was always carried out at least two hours after the last meal. None of the subjects were under the influence of any medicine which affects the cardiovascular system.

RESULTS

The most frequent response to smoking was an increase in heart rate averaging 10 beats per minute. The maximum increase was 28 beats per minute. In three instances no appreciable change in heart rate occurred. Gross changes in the RS-T segment were recorded twice. These will be discussed in detail later. The amplitude of the T waves in the remaining fourteen patients were measured from the T-P isoelectric level and were corrected for errors in the standardization of the electrocardiograph. A decrease in amplitude of 1 mm. or more in one of the standard leads was present in six instances; the maximum decrease was 2.0

mm. in Lead III and was associated with inversion of a previously upright deflection. In five patients the decrease in amplitude was less than 1 mm. while in three there was an increase in the height of T of less than 1 millimeter. Although these changes were small, their magnitude was directly proportional to the increase in heart rate. This relation has been noted previously.[20,63]

Two 38-year-old men, who presented no objective evidence of cardiovascular disease but complained of precordial pain on exertion, exhibited T-wave changes after smoking similar in character but of lesser degree than those resulting from exercise in one case, and from exercise or anoxemia in the second case. These two cases have been reported in detail in a previous paper.[64]

A number of the fourteen patients who presented T-wave changes associated with an increase in heart rate complained of tingling and coldness of the fingers and toes, sweatiness, nausea, and "dullness in the chest" not typical of angina pectoris.

CASE 1.—A practicing physician first came to the hospital in April, 1929. A diagnosis of psoriasis was made. At that time the blood cholesterol was 178 mg. per cent and the blood Wassermann was negative.

His next visit was in March, 1936, when he was 60 years of age. He then complained of a burning epigastric sensation which occurred when the stomach was empty and which was relieved by alkalies and food; there were frequent episodes of water brash and "heart burn" and occasional bouts of vomiting without hematemesis. There had been no melena. These symptoms had persisted for two or three years. In the two weeks prior to this admission the patient had had an acute febrile illness during which he had been conscious of irregularity of the heart and a mild orthopnea. Physical examination revealed an initial blood pressure of 172/100 which fell to 140/80 on bed rest. The size, rate, rhythm, and sounds of the heart were normal; no murmurs were present. The tonsils were inflammed. Psoriatic changes were present over the elbows. Examinations of the blood, urine, and stool were negative. Gastric analysis showed 7 degrees free and 20 degrees total acid but no other abnormality. Roentgenographic examination of the chest and upper and lower gastrointestinal tract revealed no abnormalities. An electrocardiogram consisting of the three classical limb leads was within normal limits.

On May 24, 1944, this man was seen for the third time. He described his condition as follows: "I can't say just when the pain started but would say it was sometime since the first of the year. I never noticed it before that time and when it first started I tried to attribute it to hyperacidity from which I suffered a great deal. But it was high up under the sternum, in my jaws, and occasionally out in the deltoid muscles. I began to suspicion it was angina since it would come on and leave in a short while, not lasting long. The pain was never very bad so that I would probably take something for it; and it would usually be relieved by sitting down, bending forward, and pressing against the sternum with my hands. It seemed that exertion had very little to do with it, and I was frequently in the habit of going over to my orchard (which is a steep mountain orchard) and walking for an hour or two without precipitating an attack." This discomfort occurred as often as twenty or forty times a day and could not be correlated with any particular activity or habit. He used two packages of cigarettes per day.

The physical findings at this time were essentially the same as those recorded eight years previously. A moderate degree of peripheral arteriosclerosis was present. Over the course of a hour the blood pressure varied from 220/95 to 180/85. The blood Wassermann and Kahn tests were negative. Laboratory studies revealed no abnormalities. Orthodiagraphic cardiac measurements (Kurtz) showed the heart to be of normal size, and fluoroscopic examination demonstrated no abnormality of the heart contour or lung fields. The thoracic aorta was dilated to a moderate degree.

An electrocardiographic study consisting of the standard and unipolar limb leads and multiple unipolar chest leads from a series of points extending from the right border of the precordium

around the left chest to the scapular line showed no definite abnormalities (see Fig. 1). A few minutes afterward, while the electrocardiographic film was being developed and inspected, the patient began to smoke a cigarette. After only a few puffs he remarked that a squeezing substernal pain, an aching at the angle of both jaws, and a choking sensation had developed. A second electrocardiograph was immediately taken. However, the discomfort lasted only two or three minutes and disappeared before all leads were recorded. This tracing showed that, although

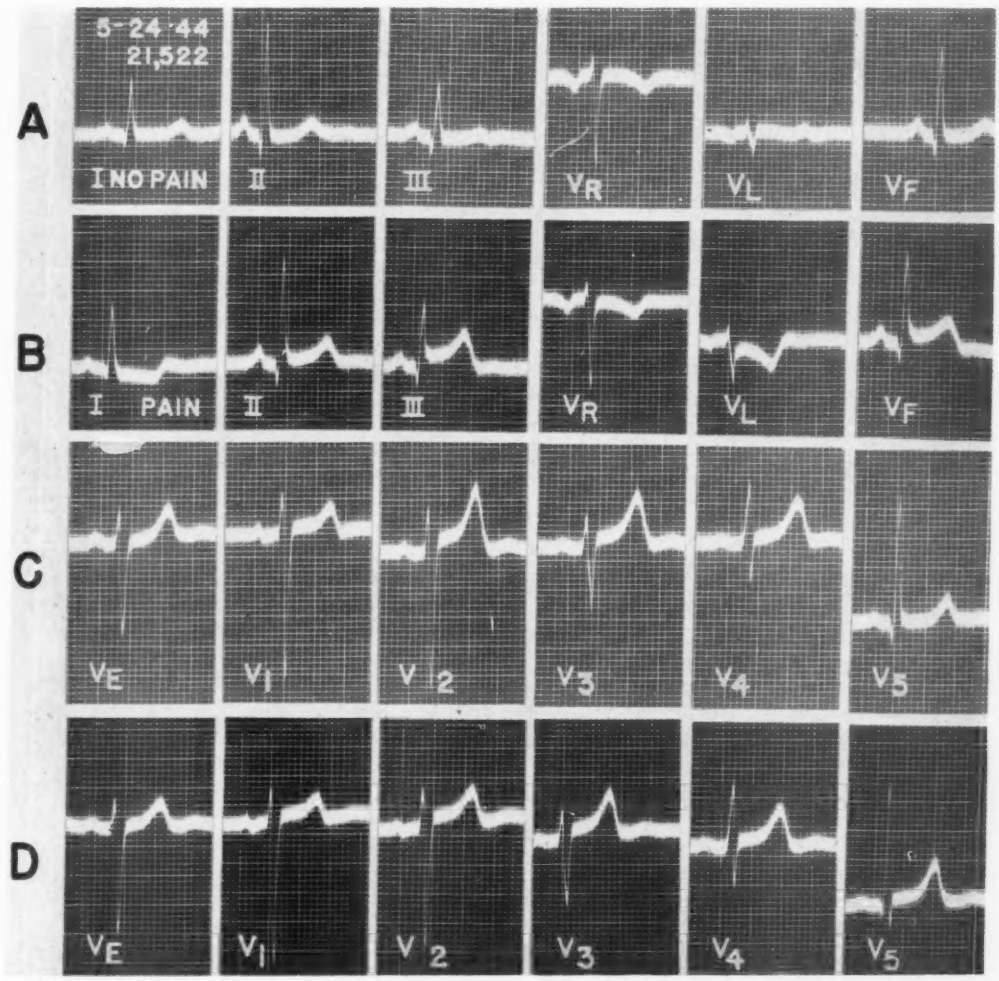

Fig. 1.—Case 1. Electrocardiograms taken before and during anginal seizure precipitated by smoking a cigarette. *A*, Limb leads before and, *B*, during smoking. *C*, Unipolar chest leads before and *D*, during smoking. Leads V_6, V_7, and V_8 are not shown.

the heart rate had not changed from the control speed of 57 beats per minute, pronounced RS-T depression in Lead I and RS-T elevation in Leads II and III had appeared. The unipolar limb and chest leads, however, showed no RS-T displacement, although they were obtained as quickly as the recording of from eight to twelve beats per lead permitted. While still recumbent, the patient then smoked another cigarette. After he had inhaled only two puffs, the discomfort

returned. He was asked to continue smoking, in spite of the pain, while another complete set of limb and chest leads was obtained. The discomfort continued while he smoked and disappeared within a few minutes after finishing the second cigarette. The discomfort was "not severe." No blood pressure determinations were made during the paroxysm.

The electrocardiograms obtained during the second episode of discomfort are reproduced in Fig. 1. The standard leads show RS-T displacement identical with that obtained during the first paroxysm. The unipolar limb leads also show RS-T displacement, although it was not recorded in these leads during the previous seizure. After correction for standardization, the unipolar chest leads exhibit slight reduction in the amplitude of the T waves in Lead V_1, moderate reduction in Leads V_2 and V_3, slight increase in Leads V_4, V_5, V_6, and V_7, and no change in Lead V_B.

An intracutaneous test, using extracts of tobacco of ten popular brands of cigarettes, produced a wheal approximately 1 cm. in diameter and without pseudopodia. This reaction was interpreted by Dr. Oscar Swineford as being of questionable significance.

The patient was informed of the significance of the foregoing observations, but he was not convinced that his symptoms were precipitated by smoking. While driving home he smoked six cigarettes and experienced the same discomfort each time. Finally, having convinced himself that his seizures were induced by smoking, he ceased smoking altogether.

In a letter dated March 13, 1945, he wrote: "In spite of doing everything that you told me not to do except smoking, I have just gotten along fine, haven't had a pain. Work sixteen hours a day, eat irregular, pull the mountains or stairsteps with no discomfort whatever."

CASE 2.—A passenger train conductor, aged 62 years, was first seen as an outpatient on May 29, 1944. Six months previously he noted for the first time a squeezing substernal sensation associated with choking and pain at the angles of both jaws. It occurred in the evening when he was walking up a slight incline on his way home from work. This discomfort would promptly subside with rest or if he took nitroglycerin. In the succeeding months it appeared at more frequent intervals and was precipitated by progressively smaller amounts of exercise. Dyspnea did not accompany these episodes of pain. Large meals decreased the amount of exercise required to induce them. Approximately four weeks before he came under observation, the symptoms, previously associated only with exertion, began to appear regularly just after he lay down in bed at night and made it necessary for him to sit up or to take nitroglycerine for relief. The patient was not aware of any relation between smoking and the onset of discomfort.

His only other complaint was long-standing "gaseous indigestion" after meals. This symptom was relieved by belching initiated by sodium bicarbonate. He also stated that he had been informed a number of years previously that he had "high blood pressure." Nocturia of two or three times was present.

On examination, the heart was of normal size, a soft systolic murmur was present at the apex, and there was slight accentuation of the aortic second sound. The blood pressure was 150/70. The peripheral areteris were markedly sclerotic and tortuous. The eye grounds were not unusual. The liver edge was 2 cm. below the right costal margin on inspiration but was not tender. The lung fields were clear on fluoroscopy. No dependent edema was present. Examinations of the urine and blood were normal. The Wassermann and Kahn tests were negative. Orthodiascopy (Kurtz) showed that the area of the cardiac silhouette, in the frontal plane, was 15 per cent above the predicted normal for men of the patient's height and weight. This finding, however, was interpreted as within normal limits. There was a slight degree of dilatation of the thoracic aorta.

Routine electrocardiographic studies made with the subject recumbent and consisting of the classical leads, unipolar limb leads, and chest leads V_2, V_4, and V_5 were within normal limits. While still recumbent the patient was given a cigarette. Shortly after inhaling only a very few puffs he complained of severe squeezing substernal pain and of choking and aching at the angles of both jaws. The discomfort subsided in about ten minutes after he stopped smoking. Electrocardiographic tracings obtained while the discomfort was present show a slight increase in the heart rate, a decrease in the amplitude of the T waves, and depression of the RS-T segment, most pronounced in the chest leads.

After this information was obtained, the patient was again questioned as to the circumstances under which he usually experienced chest pain, and especially in regard to the effects of smoking. He stated that for several years he had been in the habit of smoking only two cigarettes a day, but these were consumed just before he retired at night. He insisted that he had never associated the chest discomfort with smoking.

On the following day, May 30, 1944, further electrocardiographic studies were carried out. Standard and unipolar limb leads, and unipolar chest leads from a series of points extending from the right sternal border around the left chest to the left scapular line, were within normal limits (Fig. 2). The subject then smoked his favorite brand of cigarettes while Lead V_5 was recorded continuously for two minutes and thereafter at two-minute intervals. This lead was chosen because it had shown the most pronounced changes on the previous day. A depression of the RS-T segment, measuring about 0.5 mm., was first noticeable one minute after the subject began to smoke (Fig. 3). However, chest discomfort did not appear until one minute later when the RS-T depression increased to 1.5 millimeters. The subject continued to smoke for twenty minutes, in spite of severe discomfort, and consumed several cigarettes. In addition to the symptoms previously described, he noted numbness of the right hand which occurred twenty minutes after he began to smoke. At this time he stopped smoking and 1/100 gr. of nitroglycerine was administered. The pain subsided gradually over the next thirteen minutes and ceased thirty-three minutes after it first came on. The RS-T depression in Lead V_5 increased to a maximum of 2.0 mm. approximately ten minutes after the onset of pain. The heart rate before smoking was 76 per minute. During the period of discomfort it varied between 84 and 94 per minute and, after the administration of nitroglycerine, it did not increase but gradually returned to the control level. No blood pressure readings were made.

A second complete set of tracings taken between twelve and twenty minutes after the beginning of the test shows changes identical with those exhibited by the curves of the previous day. It displays depression of the RS-T segment in Leads I, II, III, V_L, V_F, V_2, V_3, V_4, V_5, V_6, V_7, and V_B and elevation of this segment in Lead V_R. The voltage of the T waves decreased in Leads I and V_L and in all the chest leads but increased in Lead II. In Lead III the originally negative T waves became positive. Intracutaneous tests with tobacco extracts gave results similar to those obtained in Case 1.

The patient was seen for the last time in March, 1945. He had limited his activities and had discontinued the use of tobacco. He was taking aminophylline; nevertheless his attacks continued to occur with about the same frequency.

A patient previously reported by Wilson and Johnston[2]* was recalled and was re-examined on July 11, 1946. This man, an attorney, now 57 years of age, developed angina pectoris in 1938. The paroxysms were not related to emotion or to exertion. They were most likely to occur when he had gone to bed at night. He obtained relief by standing up and by belching, which he often induced by taking sodium bicarbonate or nitroglycerine. He gave a history of gaseous indigestion from his twenty-fifth year. Studies carried out in February, 1939, showed transient electrocardiographic changes, precipitated by smoking, similar in magnitude and character to those observed in acute posterior myocardial infarction. These changes were not accompanied by subjective symptoms or by changes in the pulse rate or blood pressure. More pronounced changes of a similar kind were, however, recorded during an apparently spontaneous attack of anginal pain.

Although the patient had been advised to give up the use of tobacco, he continued to smoke an average of one package of cigarettes per day throughout the succeeding seven years. When seen in July, 1946, he stated that he had continued to have anginal attacks similar to those described, but had never noticed any relation between smoking and the onset of the paroxysms.

Electrocardiograms taken on July 11, 1946, showed only minor changes when compared with the routine tracings obtained in 1939. The T wave in Lead I had become diphasic and a small Q wave had appeared in Lead II. At this time the smoking of three cigarettes produced neither symptoms nor changes in the electrocardiograms, blood pressure, or heart rate.

*See their Case 5.

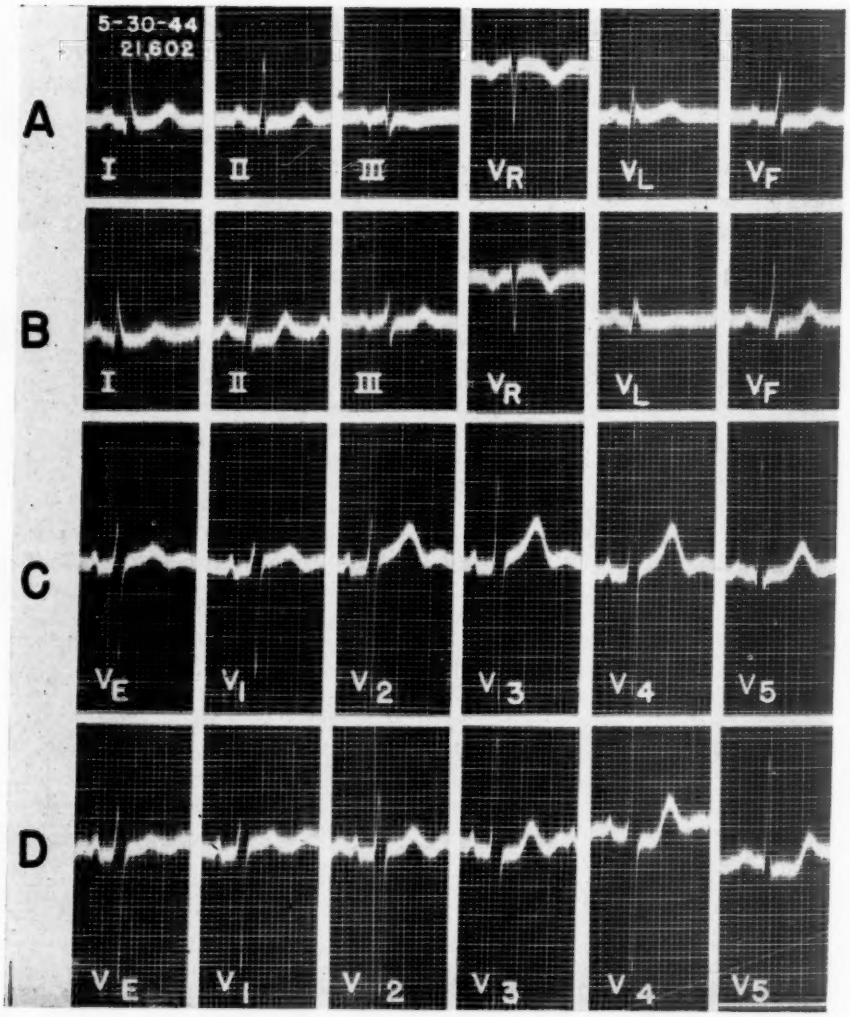

Fig. 2.—Case 2. Electrocardiograms taken before and during attack induced by smoking. *A*, Limb leads before and, *B*, during smoking. *C*, Unipolar chest leads before and, *D*, during smoking.

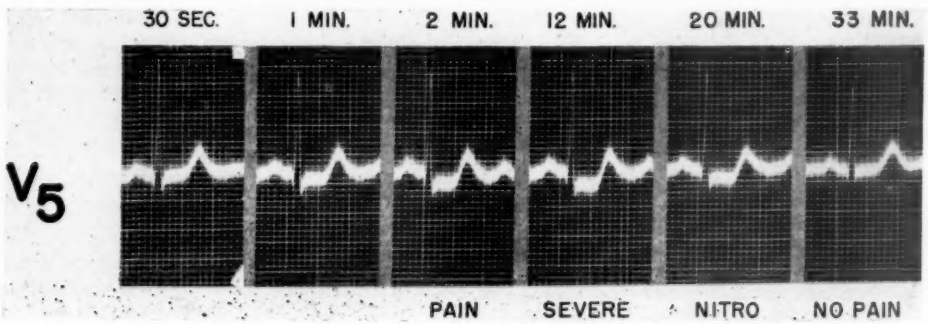

Fig. 3.—Case 2. Serial tracings of Lead V_5 taken before, during, and after anginal attack precipitated by cigarette smoking. No change from control (see Fig. 2, *C*) until one minute after subject began to smoke. Pain appeared two minutes after smoking started, right hand became "numb" at eighteen minutes, and subject ceased smoking and took 1/100 gr. nitroglycerin at twenty minutes; complete disappearance of pain 33 minutes after the subject began smoking.

DISCUSSION

Of the sixteen patients with angina pectoris on whom data are presented in this study, eleven showed an increase in heart rate and minor T-wave changes after smoking. The magnitude of the changes in the T wave was proportional to the increase in rate. Others[20,63] have observed this relation which probably represents a normal physiologic response. It has been suggested that these T-wave changes are due to the direct action of nicotine on the heart muscle fibers,[41] but we do not believe that there is much support for this view in the evidence available.

In two patients smoking induced the classical symptoms of angina pectoris accompanied by electrocardiographic changes diagnostic of pronounced myocardial ischemia.

Theoretical and experimental studies[65,66] indicate that injury which affects chiefly or predominantly the subendocardial muscle gives rise to RS-T segment depression in the unipolar leads taken with the exploring electrode adjacent to the epicardial surface of the part of the ventricular wall involved, whereas subepicardial injury produces RS-T elevation under similar circumstances. In the case of the unipolar right arm lead (V_R), the exploring electrode faces the basal ventricular orifices and often seems to reflect the potential of the ventricular cavities. The ventricular complex of this lead is frequently almost the inverse of those obtained when the exploring electrode faces the epicardial surface. If the RS-T displacements in the standard leads are plotted on the Einthoven triangle, the resulting vector gives the manifest axis of injury (—I).[67,68] When the injury is predominantly subepicardial, this axis points from the center of the involved ventricle toward the center of the injured area (Fig. 4). When the injury is predominately subendocardial it points in the opposite direction (Fig. 5).[68] Unfortunately, this type of analysis is complicated by a number of factors and possibilities that have not been fully developed. Some of these factors will be discussed at greater length in a subsequent paper.

When the electrocardiographic changes in Case 1 are analyzed by simple inspection of the unipolar limb leads or by the principles of the Einthoven triangle, the RS-T displacement suggests ischemia of the posteroseptal subepicardial muscle, which is irrigated by the right coronary artery (Fig. 4). The relatively minor changes in the T waves of the chest leads during the anginal attack were not accompanied by a change in heart rate. These changes probably reflect the influence of the ischemic area on the posteroseptal wall if it can be assumed that the same conditions were present when both the limb and chest leads were obtained. The failure of the heart rate to rise suggests that the work of the heart was not significantly increased during the paroxysm. Moreover, the absence of exertional heart pain supports the view, in this particular instance, that an increase in cardiac work was not the sole or even the chief factor inducing anginal seizures. It seems necessary to assume that the series of events described were a consequence of spasm of the right coronary artery or its branches.

In Case 2 there was concordant RS-T displacement without significant QRS changes during the anginal paroxysms precipitated by smoking. This suggests

a more widespread ischemia. Leads in which the exploring electrode faced the epicardial surfaces of the ventricles show RS-T depression, whereas in the unipolar right arm lead (V_R), which often reflects the potential variations of the ventricular cavities, there is RS-T elevation (Fig. 2). The axis of injury points

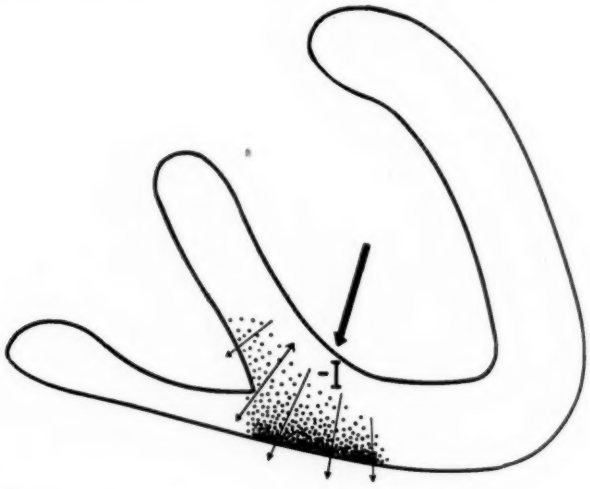

Fig. 4.—Case 1. Diagram representing hypothetical location of predominate myocardial ischemia induced by smoking and axis of injury (–I).

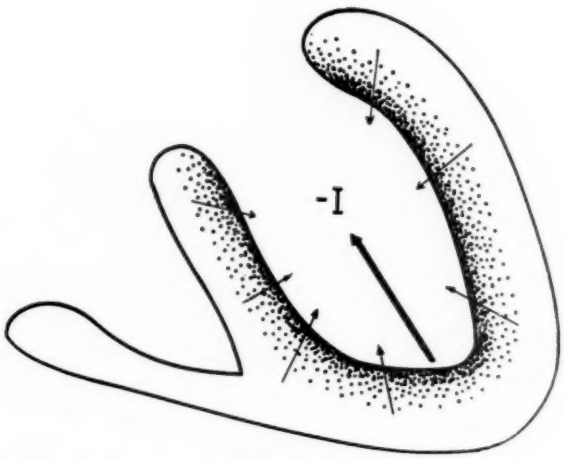

Fig. 5.—Case 2. Distribution of hypothetical ischemic region indicated by shaded area. Position of axis of injury (–I) during anginal seizure precipitated by smoking.

from the apex toward the center of the left ventricle (Fig. 5). These findings are consistent with uniform ischemia of the greater portion of the subendocardial muscle of the left ventricle. Such changes may be the result of generalized coronary spasm or spasm of the subendocardial arteriolar plexus.

Concordant RS-T segment depression in the standard leads is the most frequent electrocardiographic phenomenon accompanying anginal attacks induced by exercise[69] and anoxemia.[70] The majority of the relatively few electrocardiograms that have been taken during spontaneous anginal seizures show a discordant type of RS-T displacement.[2,54,69,71-73]

The follow-up on Wilson and Johnston's Case 5[2] is presented to show that in a case of proved tobacco angina the patient may lose his sensitivity to tobacco and still continue to experience pain unrelated to exercise.

It is interesting to note that all the patients who exhibited striking electrocardiographic changes on smoking had complained of "gaseous indigestion," suggestive of peptic ulcer, for a long time prior to the development of angina pectoris. This was also true of the two patients of Wilson and Johnston.[2] The possibility that there is a relation between diseases of the coronary arteries and the abdominal viscera has received considerable attention in the past few years.[74] Since both myocardial infarction and peptic ulcer have been produced in experimental animals by vagal stimulation,[60] it may be that these two conditions have one etiologic factor in common.

We wish to emphasize that in an unselected group of sixteen patients with angina pectoris, two habitual cigarette smokers with no previous suspicion of tobacco sensitivity developed typical anginal seizures accompanied by electrocardiographic changes indicating severe myocardial ischemia while smoking their usual brand of cigarettes. The evidence points to spasm of some part of the coronary arterial tree as the mechanism through which smoking induced paroxysms in these two patients. However, these findings by no means rule out the probability that in other patients smoking may precipitate attacks of angina pectoris by increasing the work of the heart.

In our experience, the clinical history and the clinical data routinely collected rarely suggests that smoking has an important bearing upon the symptoms in the course of the patient's illness in angina pectoris and other forms of coronary artery disease. But the circumstances which led to the discovery of a relation between the anginal attacks and the use of tobacco in two patients of this series and in two patients studied by Wilson and Johnston[2] suggest the possibility that this habit may play a more important role in these disorders than has been suspected heretofore. Routine smoking tests with electrocardiographic observations on patients with angina pectoris, even in the absence of a history of tobacco sensitivity, may help to decide this question.

CONCLUSIONS

1. In sixteen patients with angina pectoris, electrocardiograms were taken while the patient was smoking cigarettes of the brand to which he was accustomed. One instance of pure tobacco angina was discovered. In another instance the pain was precipitated by exertion and by tobacco. Neither patient had suspected that his symptoms were in any way related to smoking.

2. In these instances coronary spasm induced by smoking appeared to be the cause of the anginal seizures not related to exertion.

3. Minor changes in the T wave induced by smoking usually represent a physiologic response to an increase in the heart rate and not to myocardial ischemia. This phenomenon occurs in patients with angina pectoris as well as in normal subjects but is not associated with anginal pain.

4. The cardiovascular effects of tobacco smoking vary greatly from person to person and in the same person from time to time.

5. It is possible that the use of tobacco plays a more important role in determining the symptoms of coronary disease than has been realized in the past.

The authors wish to express their appreciation to Dr. Frank N. Wilson for his help in the preparation of this paper.

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THE TECHNIQUE OF FETAL ELECTROCARDIOGRAPHY

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INTRODUCTION

MODERN fetal electrocardiography is a highly successful and intriguing technique in search of useful clinical applications. Since the first successful series of cases was presented by Strassmann in 1938,[1] there have been a number of further reports. All the authors are enthusiastic over the relative ease of obtaining tracings of the fetal heart potentials, and many clinical applications have been suggested. Nevertheless, in the past four years there has been only one report of a series of fetal electrocardiograms in the English literature. The readily available and reliable procedures of auscultation of the fetal heart and x-ray of the maternal abdomen leave only a limited field of application for fetal electrocardiography. Furthermore, the records produced by the standard unmodified electrocardiograph may be difficult to read. Ward and Kennedy,[2] however, demonstrated that the electroencephalograph could be used without modification to record fetal deflections in a large percentage of cases. Although the electroencephalograph is now standard apparatus in many large hospitals, no further use of the method has been reported, either for routine series, or for study of the rare cases where electrocardiography alone can supply the needed obstetrical information.

The purpose of this report is (1) to present the second series of cases in which the electroencephalograph has been used to record the fetal electrocardiogram, (2) to suggest a standardized technique for fetal electrocardiography, (3) to review the literature on the characteristics of the fetal electrocardiogram and the problems involved in its recording, and (4) to evaluate the clinical applications of the technique.

METHOD

Twenty-five patients were selected at random from those attending an antepartum clinic. They were placed in the supine position, with a low pillow under the head. Standard electrocardiograph electrodes (1½ x 2½ inches) with the rubber straps removed were coated with electrode jelly and placed on the abdomen at sites that had been rubbed with electrode jelly. The electrodes were held in place with six inch strips of adhesive tape. The positions of the electrodes were the right and left upper quadrants and the midline at the superior

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limits of the uterus, and the suprapubic region just above the pubic escutcheon. These electrodes were led into the terminals of a four channel push-pull amplifier type electroencephalograph by means of the usual fine electroencephalograph electrode connection wires. The three leads used routinely and recorded simultaneously were right upper quadrant to suprapubic region, midline upper abdomen to suprapubic region, and left upper quadrant to suprapubic region. The polarity was such that when the superior electrode was negative with respect to the inferior electrode, an upright deflection was recorded. The patient was allowed to rest quietly after adjustment of the electrodes for about five minutes, and then the record was standardized and recording begun. If inspection of the tracing as it was being recorded failed to reveal readily apparent fetal deflections, the placement and connections of the electrodes were rechecked, and the recording was continued intermittently at two to three minute intervals with increasing amplification. After about ten minutes the tracing was discontinued.

Frequently tracings that appear negative on casual inspection reveal small deflections, consistent in direction, shape, and spacing, amid the irregular variations in the baseline caused by artifacts. Small fetal deflections are most readily detected when they are superimposed upon the maternal P and T waves, and thus alter the contour of the maternal waves.

RESULTS

A total of twenty-eight tracings was taken on twenty-five women in the last five lunar months of pregnancy. Of these records, twenty-three, or 82 per cent, were positive, while one tracing was doubtful, and four tracings were negative for fetal deflections. One patient delivered as a breech one week after the recording of upright fetal deflections (Fig. 1). One record showed two independent sets of fetal deflections in a proven case of twins (Fig. 2).

The fetal and maternal heart rates were measured at the beginning and end of each tracing and were found to vary independently. In twelve cases, one heart slowed while the other increased in rate; in eight cases both maternal and fetal heart rates increased or decreased together; in four cases only a single measurement of rate could be made. The sex of the fetus had no effect on the heart rates. The average rate for males (fifteen cases) was found to be 142 and the average rate for females (nine cases) was 143. The average change in rate from beginning to end of the tracing for males was 11 beats per minute, while that for females was 14 beats. No significant change in the rate of the fetal heart was observed during the course of the last five lunar months of pregnancy.

Except for moderate degrees of sinus arrhythmia, no unusual rhythms were noted. Smoking produced showers of premature beats in one patient, but had no effect on the fetal heart other than a very slight increase in rate.

The average voltage of the fetal deflections was found to be 7 microvolts. In no tracing was there any significant increase in the duration of the fetal deflection beyond 0.04 second.

The height-weight ratio (height in inches divided by normal weight in pounds) was determined for women in the sixth to eighth months. Eight women

with positive tracings had an average ratio of 0.48 while five women with negative tracings had an average ratio of 0.47. Although these groups are very small, it does not appear that bodily habitus was an important factor in determining the incidence of negative tracings.

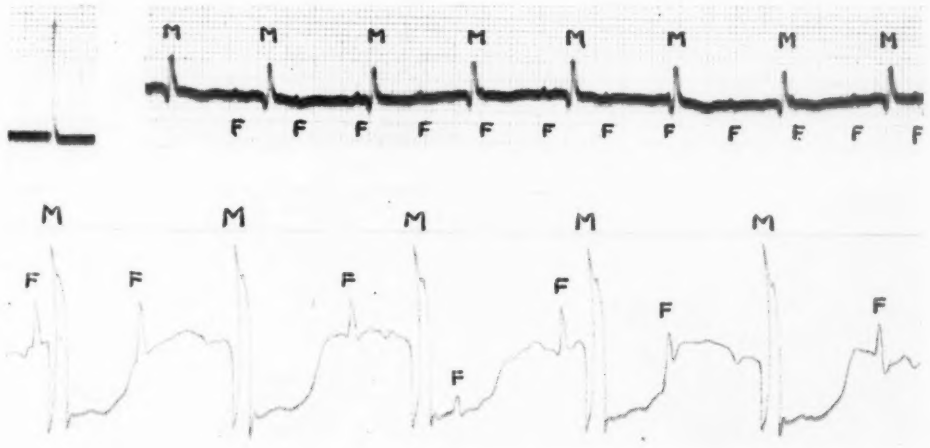

Fig. 1.—Breech presentation.

Tracings taken at term from a woman whose x-ray film showed a breech presentation and who delivered as a breech seven days later.

Upper tracing taken with standard electrocardiograph with approximately double standardization. Upright fetal deflections measure less than 1.0 millimeter.

Lower tracing taken with electroencephalograph from the same electrodes shows fetal deflections measuring 8.0 mm.

M represents maternal deflections and *F* the fetal deflections.

Fig. 2.—Tracing of twins.

Tracing shows two independent sets of fetal deflections. *M* indicates maternal deflections (QRS) while *f* indicates monophasic fetal deflections, downward directed, of a vertex presentation. *F* indicates diphasic fetal deflections with initial positive wave indicating breech presentation.

X-ray taken fifteen minutes after the tracing showed twins, one a breech and the other a vertex. The patient delivered a breech and a vertex three days later.

DISCUSSION

The various series of fetal electrocardiograms reported in the literature differ widely in many details of technique. Analysis of these variations shows that the simplest procedures apparently yielded the best results. This is fortunate, for if fetal electrocardiography is to be used clinically in the study of the infrequent cases in which it alone can yield valuable information, a simple and easily applied technique must be available.

Standardization of Technique.—

1. Recording Instrument: Specially designed recording apparatus is not readily available to the obstetrician. Such apparatus includes the valve amplifier used with the string galvanometer by Maekawa and Toyoshima,[3] the balanced input amplifier introduced into the circuit of a valve electrocardiograph used by Bell,[4] the specially designed "Cardiette" with a sensitivity of 6 cm. per millivolt used by Bernstein and Mann,[5] and the single stage resistance-coupled preamplifier used by Goodyer, Geiger, and Monroe.[6] In many large hospitals, however, the standard electroencephalograph apparatus is available for routine use. This type of apparatus has a far greater sensitivity than the most powerful of the specially designed equipment, giving an indicated deflection of up to 100 cm. per millivolt. In 1942, Ward and Kennedy[2] demonstrated the ready application of the electroencephalograph to fetal electrocardiography. Lindsley[7] had previously used this type of apparatus in a single case in 1936, but did not publish his report until 1942. The series reported in this communication was begun before these two papers were noted and was completed in 1943.

While the electroencephalograph is the most sensitive standard instrument available, the standard electrocardiograph, adjusted to normal,[1,8] double,[9] or triple[10] standardization, has been used to record the fetal electrocardiogram. Only in the last two or three months of pregnancy, however, can the electrocardiograph be used with any degree of success. The superiority of the electroencephalograph over the electrocardiograph with approximately double standardization (1.7 cm. per millivolt) is shown in Fig. 3. The fetal deflections are much larger, clearer, and therefore easier to identify. The mechanical inertia of the pens tends to smooth out irregularities in the baseline produced by artifacts. The recording of all leads simultaneously shortens the procedure and allows for more certain identification of very small deflections by comparison of two or more leads. Furthermore, since the record is produced by ink-writers on paper, the results of the test are immediately available, and for special purposes long recordings may be made at little cost.

2. Selection of Leads: The early workers used rectal or vaginal leads in conjunction with abdominal leads.[11-13] This was later followed by the use of the standard limb leads taken from the proximal portions of the extremities.[1] Bell[4] and Mann and Bernstein[9] found that leads taken directly from the maternal abdomen were superior to limb leads, since such leads gave fetal deflections of larger amplitude, with maternal deflections reduced in amplitude, so that the sensitivity of the recording device could be increased. Fig. 3 shows this superiority of abdominal over limb leads. Most of the more recent series have been recorded from abdominal leads.

The location of the abdominal electrodes have varied in the different reports. Almost all authors have used a vertical lead from the epigastrium or umbilical region to the symphysis or suprapubic region. Diagonal leads have been taken from the epigastrium to the lower quadrants, from the upper quadrants to the suprapubic region, or from the upper quadrants to the diagonally opposite lower

quadrants. Transverse abdominal leads have also been used. The vertical and two diagonal leads are all necessary, for as shown by Goodyer and associates[6] fetal deflections may appear in only one of these three leads. His use of the diagonal leads, from one upper quadrant to the opposite lower quadrant, is logical, since the greater angle between those leads and the vertical lead increases the likelihood of picking up weak potentials from longitudinal or near-longitudinal presentations. The superior electrodes should be placed at the upper limits of the uterus as determined by palpation. The lower midline electrode should be placed just above the pubic hairline to insure good contact. Abdominal leads should be referred to by letter, rather than designated "Lead I," which may be confused with the standard limb leads.

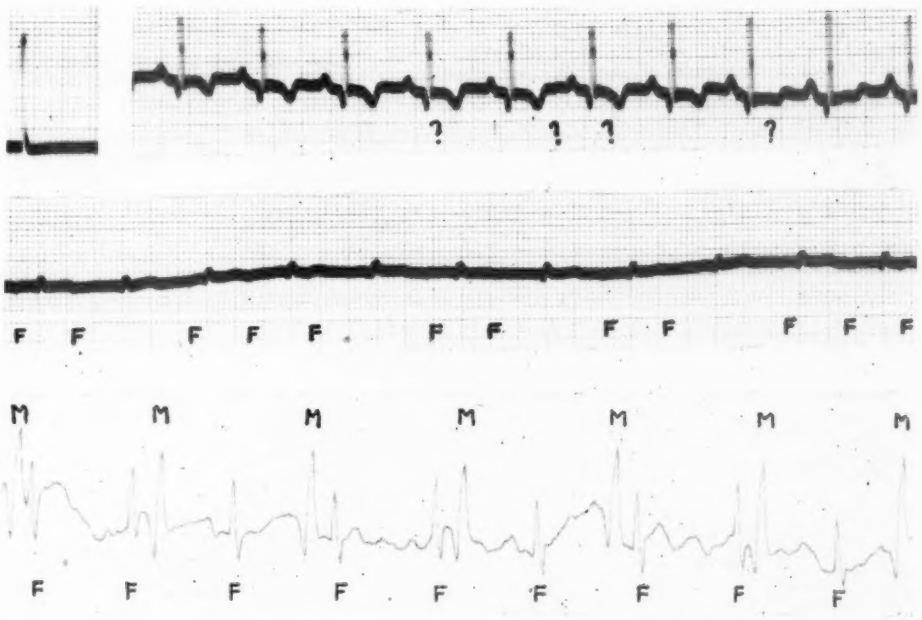

Fig. 3.—Comparison of leads and recording apparatus.

Top tracing taken with electrocardiograph at double standardization using standard limb Lead II, with electrodes at proximal portions of the limbs. A few irregularities are present in the baseline that cannot be positively identified as fetal deflections.

Middle tracing taken with electrocardiograph at approximately double standardization using abdominal leads. Tiny fetal deflections are visible that recur at regular intervals when not hidden by the maternal complexes.

Bottom tracing taken with electroencephalograph from same abdominal electrodes as middle tracing. Waves are altered in contour due to pen inertia. Fetal deflections are large, and the initial positive wave indicates a breech presentation, but no x-ray was available for confirmation. Patient was in sixth lunar month, and delivered at term as a vertex.

These tracings indicate the superiority of abdominal over limb leads, and of the electroencephalograph over the electrocardiograph for recording fetal electrocardiograms.

Lindsley[7] pointed out that by varying the placement of the electrodes, it is possible to eliminate the maternal deflections from the record. This is confirmed in the tracing shown in Fig. 4. There is a progressive diminution in the

amplitude of the maternal deflection as the superior midline electrode is brought closer to the suprapubic electrode. The lowest pen records only the fetal deflections, with no maternal deflections identifiable. There is no advantage to be gained by eliminating the maternal complexes. In fact the maternal complexes are needed in order to prove the fetal origin of waves that might otherwise be mistaken for unusually small and rapid maternal deflections.

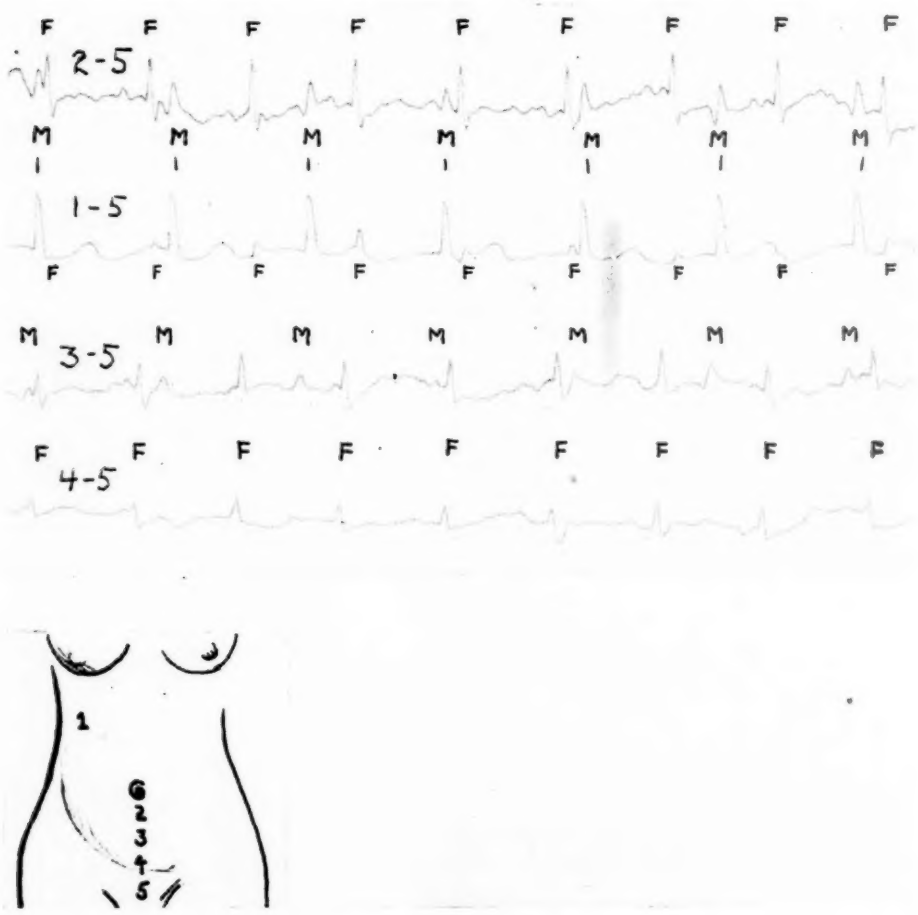

Fig. 4.—Elimination of maternal deflections.

The pens record four leads simultaneously. The location of the electrodes is illustrated in the diagram.

The second pen records from Position 1 to Position 5, one of the three routine abdominal leads. Large maternal and small fetal deflections are indicated by *M* and *F*, respectively.

The first pen records from Position 2 to Position 5, and shows the fetal deflections larger than the maternal.

The third pen records from Position 3 to Position 5, the superior electrode approaching the fixed interior electrode. Maternal deflections made out with difficulty.

The fourth pen, recording from Position 4 to Position 5 shows only fetal deflections, with maternal waves indistinguishable from baseline irregularities.

Lindsley's explanation for the blanking out of the maternal deflections is that the linea alba and aponeuroses of the abdominal muscles shunt the maternal currents. A more likely explanation is the negligible drop in potential of the maternal current taken over a short distance so far from the point of origin. At the same location, however, the electrodes are much closer to the origin of the fetal current, which shows a large drop in potential over a short distance.

3. Minor Points of Technique: Alteration in the time constants of the electroencephalograph used by Ward and Kennedy,[2] and increase in the paper speed in the string galvanometer used by Strassmann[10] have been suggested as means of increasing the incidence of positive results. Having the patient void before the test eliminates the possibility of a full bladder short-circuiting the fetal potentials. Use of the supine position with a low pillow under the head eliminates much tremor due to contraction of the abdominal musculature. Most workers advise a short period of rest before recording is started. Frequently the fetal deflections can be found only near the end of the tracing when artifacts due to somatic tremor and other causes diminish.

The standard electrodes used in electrocardiography are readily applicable to this technique and are easily held in place by strips of adhesive tape. Electrode jelly, used in electrocardiography, is rubbed on the abdomen and spread on the electrodes, and gives results as good or better than saline dressings, which are less convenient.

The Fetal Electrocardiogram.—Although the fetal electrocardiogram as recorded by direct leads from aborted fetuses closely resembles the adult pattern,[14-16] prenatal fetal electrocardiograms, recorded from the maternal abdomen or uterus,[17] show only the initial ventricular deflections or QRS waves. The value of fetal electrocardiography in the diagnosis of fetal arrhythmias is thus almost nullified by the absence of recorded P waves.

Fetal deflections consist of either a single sharp spike (Fig. 5) or low curve if small, or of diphasic waves (Fig. 3). One tracing recorded by Ward and Kennedy[2] and another by Putz and Ulrich[18] show complexes consisting of three components: a short positive wave followed by a deep negative spike, and then a short positive wave. The most variable of the factors governing the direction as well as amplitude of the fetal deflection is probably the position of the fetus in the uterus, or more concisely, the position of the fetal heart with respect to the electrodes recording the deflections. It has been assumed that when the superior electrode is negative with respect to the inferior electrode and an upright fetal deflection is inscribed, the position of the heart is base uppermost and apex pointing downward, or a breech presentation. Breeches have been diagnosed by this means, and one worker claims that "the most accurate method of detecting presentation is by means of a positive electrocardiogram."[8] Strassmann and Mussey[19] noted that frequently the initial negative deflection of vertex presentations is followed by a short positive deflection, while in breeches, the initial positive deflection is often followed by a short negative deflection. However, there are other factors affecting the fetal electrical axis that by the same token affect the direction as well as amplitude of the recorded deflections. These

include the relative size of the two sides of the heart, the difference in contraction timing between the two sides, and the position of the heart inside the fetal thorax. The full description of the recorded fetal complexes and their significance awaits careful study with a sensitive recording apparatus such as the electroencephalograph, in conjunction with x-ray examination and a study such as Bell performed[4] consisting of a series of crown-rump leads on the newborn infants.

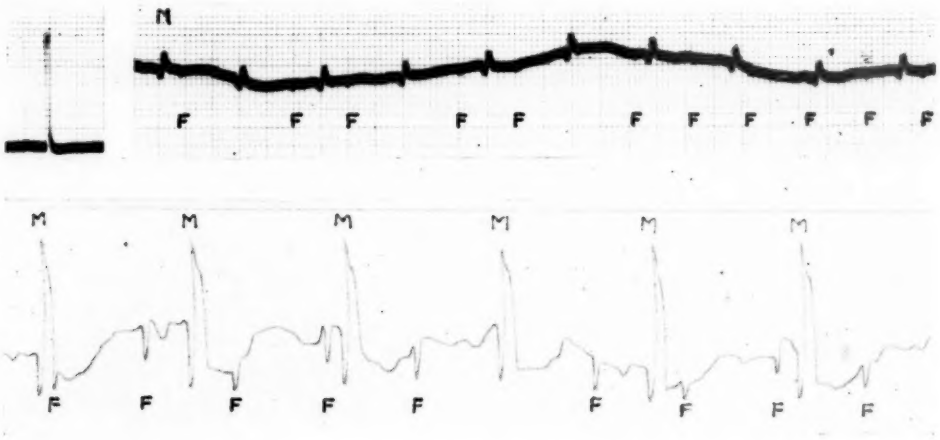

Fig. 5.—Vertex presentation.

Upper tracing taken with electrocardiograph at approximately double standardization using abdominal leads. Fetal deflections measure 0.5 millimeter.

Lower tracing taken with electroencephalograph from same electrodes. Fetal deflections measure up to 6.0 millimeters.

The amplitude of the fetal deflections obtained by Ward and Kennedy[2] averaged 30 microvolts. Goodyer[6] recorded the largest fetal deflections of 70 microvolts. In this study the waves averaged only seven microvolts. Extracardiac factors that may influence the amplitude of the fetal deflections are the varying thickness of the abdominal wall and the other structures, and conducting media between the fetus and the electrodes. Even more important, however, is the angle between the electrodes and the axis of the fetus. The duration of the fetal deflections varies between 0.02 and 0.04 second.

It is known that marked variations in fetal rate occur without apparent cause, and that the rate is increased by fetal movement, palpation of the fetal body, fasting, asphyxia, and hemorrhage.[20] Fever,[21] vibratory stimuli and loud sounds,[22] smoking,[23] and inhalation of amyl nitrite by the mother[24] also increase the rate, while uterine contractions and pressure on the fetal brain[20] decrease the rate. The effect of other drugs on the human fetal heart has apparently not been systematically determined, although fetal electrocardiography offers an ideal technique for such studies.

Although a recent textbook of obstetrics states that "experience does seem to show that girls' (fetal) hearts beat faster than boys,' "[20] none of the workers

with fetal electrocardiography or stethography have been able to demonstrate such a difference.

The relationship of the fetal rate to fetal age has not been definitely determined. Sontag and Richards[25] and Sontag and Newberry[26] reported a gradual decline in the fetal rate from the fifth month to the tenth month, save for a slight rise in the ninth month. Bernstein and Mann,[5] using the electrocardiograph, reported a gradual decline in the rate from the fourth to the eighth month, with a slight rise during the last two months of pregnancy. Goodyer[6] was unable to find any correlation between fetal rate and age.

While many workers have claimed that the fetal rate is related to the maternal rate in various constant ratios, more recent reports have been unable to confirm this.[5,6] The very great variability in the fetal rate from hour to hour[22] compared with the relatively constant rate of the normal maternal heart at rest, would not seem to permit of the establishment of any such ratio. It has been shown in the foregoing that the fetal heart rate varied in inverse relationship to the rate of the maternal heart more often than in direct relationship.

In the analysis of fetal arrhythmias, the absence of P waves in the fetal electrocardiogram makes this method of no more value than fetal stethography. Fetal arrhythmias occur far more often than has been realized. Hyman[27] has stated that arrhythmias are present in over 9 per cent of pregnancies. So-called sinus arrhythmias are found very commonly. In view of the increasing evidence for fetal respiration,[28] this arrhythmia may well be similar to the sinus arrhythmia of postnatal life which is related to respiration. However, true sinus arrhythmia is mediated through the vagus, which does not exercise cardiac control until very late in fetal life.[29]

Premature contractions, often identified as being of ventricular origin by postnatal electrocardiograms, have been described by many workers.[5,22,30-33] Unlike the premature contractions of adult life which tend to disappear on increase of the heart rate following exercise, the fetal premature contractions have been found to occur with increased frequency during the tachycardia accompanying the fetal startle reflex.[22] These fetal premature contractions are of little clinical significance, and were found to disappear a few days after birth.[27]

A third type of arrhythmia described by Hyman[27] is a gross irregularity of the fetal heart, which when pronounced suggested auricular fibrillation. It occurred in eleven cases associated with sudden interruption of pregnancy or difficulty in resuscitation of the infant after delivery.

Fenichel and Kurzrok[34] described blocked auricular extrasystoles in a fetus, which persisted after birth and were confirmed by postnatal electrocardiograms. Geiger and Hines[35] discussed the prenatal diagnosis of complete and partial congenital heart block. Plant and Steven[45] reported a case of complete A-V block in which the fetal electrocardiogram showed a rate of 56 per minute. The postnatal electrocardiogram showed complete A-V dissociation with an auricular rate of 114 and a ventricular rate of 50 per minute.

Factors Influencing the Success of Fetal Recordings.—The earliest recordings of the fetal electrocardiogram have been obtained in the sixteenth week of preg-

nancy[2,5,6,9] in a small percentage of attempts. Bernstein and Mann[5] found in their series of 153 records a sharp drop in the percentage of positive cases recorded in the seventh and eighth lunar months as compared with the preceding and subsequent months. Goodyer[6] in a series of 181 records was unable to show any significant drop in the incidence of positive tracings over that period. However, the data of these authors show a very definite decrease in the average amplitude of the fetal deflection during those two months. On compiling all the published cases amenable to analysis by lunar months of pregnancy, including the large series of Goodyer, this drop in the incidence of positive tracings can be demonstrated as shown in Table I. Out of the composite group of 482 tracings, 90 per cent of those taken in the sixth month and 92 per cent of those in the ninth month were positive, while in the seventh and eighth months only 75 per cent and 65 per cent, respectively, were positive. Application of the formula for the standard error of the difference between two proportions,[36] $\sqrt{\frac{p_1 \times q_1}{n_1} + \frac{p_2 \times q_2}{n_2}}$ shows that both the fall in positive results from the sixth to the seventh month, and the rise from the eighth to the ninth month are significant at the level of significance where the possibilities are five out of 100 that the difference might be due to chance.

The reason for this fall in the incidence of positive results is not apparent. It has been pointed out[6] that early in pregnancy the small size of the fetus compared with the relatively large amount of amniotic fluid and lack of contact between uterus and abdominal wall might account for the inability to pick up the fetal potentials. These factors do not account for the fall in positive results occurring later in pregnancy. It has been suggested[5,37] that a sudden relative increase in the amount of amniotic fluid with regard to the fetal mass during the seventh and eighth months could explain the drop in positive tracings. There is no support for this view in the available data on the volume of amniotic fluid. The amount of fluid increases progressively until the seventh month, after which it decreases in amount until term.[38] Furthermore, even hydramnios has not prevented the recording of the fetal electrocardiogram.[6,39]

Other factors that are believed to reduce the chances of obtaining positive tracings are the thickness of the abdominal wall and the interposition of the placenta. While it has been shown that fetal deflections obtained directly from the uterus are much larger than those recorded from the abdomen,[17] and while many workers have felt that obesity reduces the chances of recording fetal potentials, Goodyer and associates[6] could find no correlation between the height-weight ratio, an index of bodily habitus, and the incidence of positive results. In the current series, very little difference was found between the height-weight ratio of women yielding positive and negative tracings.

The size of the fetus is thought by some to be related to the incidence of positive tracings. Bell[4] could not confirm this and Goodyer[6] was unable to show a correlation between the fetal wave amplitude at term and the birth weights in the same cases.

TABLE I. COMPOSITE TABULATION OF POSITIVE AND TOTAL TRACINGS BY LUNAR MONTH OF PREGNANCY

AUTHOR	LUNAR MONTH OF PREGNANCY															
	3		4		5		6		7		8		9		10	
	POS.	TOT.	POS.	TOT.	POS.	TOT.	POS.	TOT.	POS.	TOT.	POS.	TOT.	POS.	TOT.	POS.	TOT.
Mann and Bernstein[9]	0	2	1	4	5	12	8	11	8	10	5	8	16	16	13	13
Bernstein and Mann[5]	0	4	3	9	11	18	28	29	14	19	14	26	26	27	20	21
Ward and Kennedy[2]	0	4	1	4	9	10	3	3	2	4	4	5	7	7	5	7
Goodyer and associates[6]	0	6	0	18	39	48	16	18	12	15	11	13	19	23	40	40
This series					0	1	3	3	3	4	3	5	3	4	11	11
Total per month	0	16	5	35	64	89	58	64	39	52	37	57	71	77	89	92
Per cent positive	0		14.3		71.9		90.6		75.0		64.9		92.2		96.7	

Only those series amenable to analysis by lunar month of pregnancy are included in this tabulation.

Applying the formula $\sqrt{\frac{p_1 \times q_1}{n_1} + \frac{p_2 \times q_2}{n_2}}$, the difference between the proportions[36] of positive tracings in the sixth and seventh month is 15.6 per cent, more than twice the standard error of 7.0. The difference between the eighth and ninth month is 27.3 per cent, more than twice its standard error of 11.5.

Apparently there are more decisive factors than thickness of the abdominal wall, amount of amniotic fluid, or weight of the fetus in influencing the incidence of positive tracings. Borter[39] suggests individual variations in tissue conductivity as the most important factor. However, it has been noted in this series as well as in those of others that the same cases in which tracings are negative on one occasion may show fetal waves of good amplitude a week or two later. The main factors governing the ability to record the fetal electrocardiogram have yet to be determined.

Factors that interfere with the recognition of recorded fetal waves include excessive somatic tremor, poor electrical contact, amplifier noise, and outside electrical interference. Fetal and uterine movements also produce electrical potentials.[40,41] All of these cause disturbances in the baseline of the tracing and tend to hide small fetal deflections. If there is marked fetal sinus arrhythmia, small deflections that might otherwise be recognized by their regular recurrence amidst the irregularly spaced baseline artifacts can no longer be identified, and such tracings would appear negative.

Clinical Applications of the Method.—While many applications of fetal electrocardiography have been suggested by those intrigued with the technique, in most cases other methods of obtaining the same information are available, which are simpler in performance and more reliable in their results. The rarity of the occasions in which fetal electrocardiography alone is indicated accounts for the lack of interest on the part of obstetricians in this technique.

1. Diagnosis of Pregnancy: Bell[4] pointed out that the recording of fetal potentials constitutes a test which unlike the biologic tests does not give false results. However, the biologic tests become positive within a two- to three-weeks' period after conception,[38] while fetal electrocardiograms do not become positive until the sixteenth week. It is only in cases where the biologic tests are positive yet pregnancy doubted, such as in hydatidiform mole or chorionepithelioma, that fetal electrocardiography might be used to aid in diagnosis. In pseudocyesis, or amenorrhea with abdominal tumors, a negative electrocardiogram would only supplement a negative biologic test.

2. Diagnosis of Multiple Pregnancy: Theoretically, multiple pregnancies may be diagnosed a few weeks sooner by electrocardiography than by any other method. X-ray examination does not become positive until the fifth month.[42] There have been six cases reported in the literature of the electrocardiographic diagnosis of multiple pregnancies. However, there have been reports of four cases of twins in which only a single fetal heart was detected, a case of triplets in which only two fetal hearts were detected, and a case of twins with hydramnios in which no fetal deflections were found. This record of about 50 per cent accuracy of diagnosis is not at all impressive compared with the reliability of x-ray diagnosis.

3. Diagnosis of Fetal Position: As pointed out earlier, upward deflections or the initial upward deflections of diphasic waves may not always signify breech presentations. Where the initial upward deflection is small compared with the

succeeding downward deflection, and the baseline irregular, the diagnosis of a breech may be missed. In Fig. 2, taken from a case of twins, shown by x-ray study to be vertex and breech, both sets of deflections are predominantly downward. On careful examination, however, a smaller and inconstant upward deflection preceding the larger downward component is found in one of the sets of potentials; that of the breech. Since anomalies of the cardiac morphology, physiology, and of the position of the heart in the fetal chest affect the electrical axis, the diagnosis of fetal position by electrocardiography is unreliable.

4. Diagnosis of Fetal Arrhythmias: Careful auscultation may reveal fetal arrhythmias, and they can be recorded for more careful study by the stethograph as well as by the electrocardiograph. The absence of P waves in the record deprives the electrocardiogram of its theoretical advantage in the diagnosis of arrhythmias. However, where funic or uterine souffle or other auditory interference prevents recording of the heart sounds, the heart potentials may still be obtained. Furthermore, use of the paper writing electroencephalograph apparatus will give long records at a minimum of expense.

5. Diagnosis of Congenital Anomalies: It has been suggested that the prenatal diagnosis of congenital cardiac anomalies might be made by the discovery of prolongation of the fetal QRS time due to the slowing of conduction around a defect in the ventricular septum. No such diagnoses have as yet been made. In one case of extensive cardiac malformation, including absence of the interventricular septum, the prenatal electrocardiogram was found to be normal.[9] In a case of the absence or imperfect development of the bundle of His with complete A-V dissociation, the fetal deflections were not prolonged.[45] On the other hand, diagnoses of congenital defects have been made by discovery of fetal murmurs, sometimes in conjunction with fetal arrhythmias.[30,32,43,44] Fetal stethography lends itself well to the accurate study of this type of case, since murmurs as well as the fetal rhythm are recorded, and is therefore to be preferred over electrocardiography in the prenatal diagnosis of congenital heart disease.

6. Diagnosis of Fetal Life: The unique value of the electrocardiograph in obstetrical practice is in the determination of fetal life in those rare cases in which fetal sounds and movement cannot be detected. The biologic tests continue to be positive for weeks after the death of the fetus, but the finding of fetal deflections is convincing proof of a living fetus. At term the incidence of positive results is between 90 and 100 per cent, depending on the technique used. Furthermore, the technique is simple and the results immediately available. Although fetal electrocardiography has not fulfilled much of its early promise, in this particular obstetrical problem it is the only method that can be relied upon to yield the necessary information.

CONCLUSIONS

1. The technique of fetal electrocardiography is both simple and practical, as shown by a suggested standard technique.

2. The use of the electroencephalograph is to be preferred to the use of specially constructed or modified electrocardiographs, since the former is available in many large hospitals, is more sensitive, and yields better results.

3. At or near term, the standard electrocardiograph adjusted to double standardization may also be used satisfactorily to record the fetal electrocardiogram.

4. The main practical application of fetal electrocardiography in obstetrics is in the diagnosis of fetal life where fetal heart sounds and movements are absent. In these cases, the procedure is rapid and reliable, with no false positive results.

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CIRCULATORY ADAPTATIONS IN AYERZA'S SYNDROME—BLACK CARDIACS

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CLINICAL and anatomic studies have led to the conclusion that Ayerza's disease is only a form of *chronic cor pulmonale with cyanosis.* It would seem now that the sclerosis of the pulmonary artery that was considered very important before is actually only secondary to the chronic bronchopulmonary ailments that determine the disease.

From a functional standpoint these pulmonary ailments lead to alveolar hypoventilation, which is the first link of a chain in the physiopathologic picture of these patients. Alveolar hypoventilation produces anoxemia with varying degrees of arterial unsaturation and also increase of the carbon dioxide tension in the blood. Arterial unsaturation leads to the increase of the erythropoietic activity of the bone marrow, thus originating hyperglobulia and an increase of hemoglobin, which added to the arterial unsaturation, determines the marked cyanosis which characterizes these patients. Thus is explained, on a physiopathologic basis, the clinical picture shown by patients who have been referred to as black cardiacs.[2-4,5,15]

Even though these studies have permitted the explanation of the physiopathogenesis of this syndrome, there exist certain facts, concerning which there are still some doubts. For example, it has not yet been explained why, if the alveolar hypoventilation is the only cause of anoxemia, the oxygen tension in the arterial blood of these patients is usually markedly lower than the alveolar oxygen tension. Neither do we know why some patients, in spite of having marked alveolar hypoventilation, never have the clinical features shown by black cardiacs.

Both these facts have induced some authors to support the theory that the clinical features of the black cardiacs only appear when the oxygenation of the blood is impeded by a disorder in the oxygen diffusion in the lungs; this disorder might be related to the much-discussed primary sclerosis of the pulmonary artery.

On the other hand, patients with Ayerza's disease present to the physician the problem of circulatory and respiratory adaptation, not thoroughly studied yet, that permits them to withstand such unfavorable conditions for so many years.

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In order to clarify these facts, we have accomplished a study on the circulatory and respiratory functions of a group of patients of this type in different periods of the evolution of the disease.

This study was made on sixteen patients with varying degrees of pulmonary fibrosis and emphysema.

A cough of long duration and repeated bronchitis were registered in the history of all patients. Eight had also suffered asthmatic attacks. All the patients presented effort dyspnea. Fourteen had marked cyanosis, and nine presented all the clinical features characteristic of Ayerza's syndrome.

In Table I the main characteristics of each patient are shown. As can be seen, eight of the patients were suffering from cardiac insufficiency when they came under our care. The diagnosis in these patients was reached through the following findings: cardiac enlargement, gallop rhythm, tricuspid murmur, hepatic congestion, and increased venous pressure. Dyspnea was considered as a symptom of cardiac failure only when it appeared during rest and in the absence of bronchial spasm. Edema, so often found in these patients, was considered as a sign of cardiac failure only when it was marked and accompanied by hepatic congestion and increased venous pressure.

DETERMINATIONS MADE AND METHODS EMPLOYED

In the analysis of the patients a study was made of the respiratory, circulatory, and blood functions, according to techniques stated and in the following order:

Lung volume and its subdivisions were determined by Christie's method,[7] modified by Robinson.[23]

Alveolar air was collected with a test tube of 20 mm. diameter and 100 c.c. capacity, with a Müller valve in one end and a three-way stopcock in the other. In patients in whom it was not possible to obtain air instantaneously, the sample was taken four seconds afterward (expulsion, more than 600 cubic centimeters).

Serial alveolar air was determined by taking samples after the exhalation of 500, 900, and 1,300 c.c. within six seconds.

Lung ventilation was determined in a gasometer of 600 liters in twenty-minute periods with measurements every minute. All volumes are expressed at 37°C., prevailing varometric pressure, and complete saturation with water vapor.

Cardiac output was determined by Grollman's[12] four-sample method.

Blood volume was determined by the Gibson and Evans'[11] technique with Evelyn's photocolorimeter.

Venous pressure was determined by the direct method: Lyons, Kennedy, and Burwell[20] technique.

Circulation time: Decholin and ether were used for the arm-to-tongue and arm-to-lung circulation times, respectively.

Arterial blood examinations were made of the arterial blood withdrawn from the femoral artery and heparinized, using the Van Slyke apparatus.

Calculation was made of the carbon dioxide tension and the pH of arterial blood by the nomogram and Cartesian chart of Henderson and associates[13] and by Henderson and Hasselbach's equation. *Free carbon dioxide in serum* was calculated with the solubility coefficient of Van Slyke and co-workers[29]; $pK = 6.11$, according to Dill, Daly, and Forbes.[10]

TABLE I. MAIN CLINICAL CHARACTERISTICS OF PATIENTS STUDIED

CASE	AGE	SEX	PULMONARY				HEART				ARTERIAL PRESSURE	DYSPNEA	CYANOSIS	EDEMA	RED CELLS
			EMPHYSEMA	FIBROSIS	ASTHMA	SCLEROSIS OF PULMONARY BRANCHES	ENLARGEMENT OF HEART	DILATATION OF PULMONARY TRUNK	DEVIATION OF ELECTRICAL AXIS TOWARD RIGHT	RIGHT HEART INSUFFICIENCY					
1 (E. A.)	60	M	+	+++	+	+++	++	+	–	–	160/80	+++	++	++	6,400,000
2 (P. C.)	46	M	+	+	+	+	+	+	+	–	130/90	++	+	–	5,800,000
3 (V. F.)	53	M	+	+	+	+	+	++	–	+	180/120	+++	++	+	6,300,000
4 (D. Fi.)	40	M	++	++	++	++	+	++	+	–	170/105	++	+++	+	7,300,000
5 (M. R.)	49	M	+++	++	+	++	–	+++	–	–	150/105	++	+	–	5,600,000
6 (F. T.)	55	M	++	+++	++	++	++	+	–	–	140/85	++	+	–	4,500,000
7 (R. A.)	35	M	++	+	++++	++	+	++	+	+	170/110	+++	++	++	6,700,000
8 (J. M.)	52	M	+	++	+++	++	+	++	–	–	135/110	+++	+++	–	6,900,000
9 (A. T.)	58	M	++	++	++	++	+	+	+	–	125/80	+++	+++	–	5,600,000
10 (M. A.)	64	M	++	++	+	++	++	++	+	+++	170/110	++	++++	+++	7,690,000
11 (F. B.)		M	++	+++	+	+++	++	+	+	++	125/70	+++	+++	+	6,400,000
12 (M. B.)		M	+++	+++	+	+++	+++	++	+	+++	135/85	+++	++++	++	6,410,000
13 (D. Fe.)	51	M	+	+	++	+	++	+	+	+++	155/110	+++	++++	+++	7,500,000
14 (L. G.)	62	M	+	+++	+	++	+++	++	–	+++	180/120	+++	+++	++++	6,900,000
15 (G. S.)	54	M	++	+++	+	+++	+++	++	+	++++	120/80	++++	++++	++++	7,400,000
16 (N. S.)		M	++	++	++	++	+	++	–	–	220/115	++	+	–	4,700,000

+, Light; ++, moderate; +++, marked; ++++, severe.

Oxygen tension in the arterial blood was calculated by interpolation in the dissociation curve, which was constructed with points to 20, 30, and 60 mm. Hg of oxygen and 40 mm. Hg of carbon dioxide, to pH 7.40. A standard curve was used in those patients in whom a dissociation curve was not constructed.

RESPIRATORY FUNCTION

Lung Volume and Its Subdivisions.—The study made of the pulmonary function demonstrated the characteristic picture of emphysema with pulmonary fibrosis (Fig. 1). In all the patients there was observed a real or relative increase

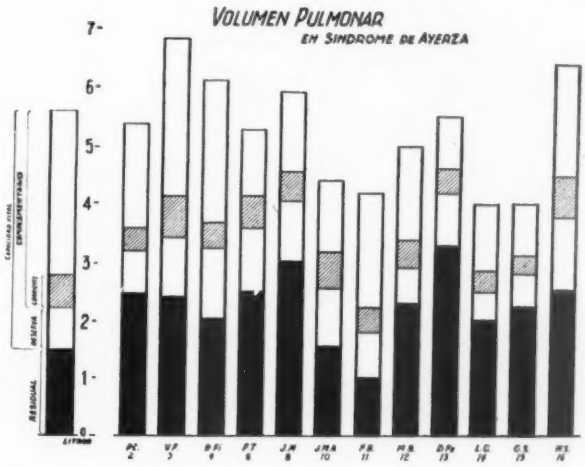

Fig. 1.—Pulmonary volume in patients with Ayerza's syndrome. The first column represents the mean normal values found in persons of more or less the same age. The following columns represent the values found in each individual case studied.

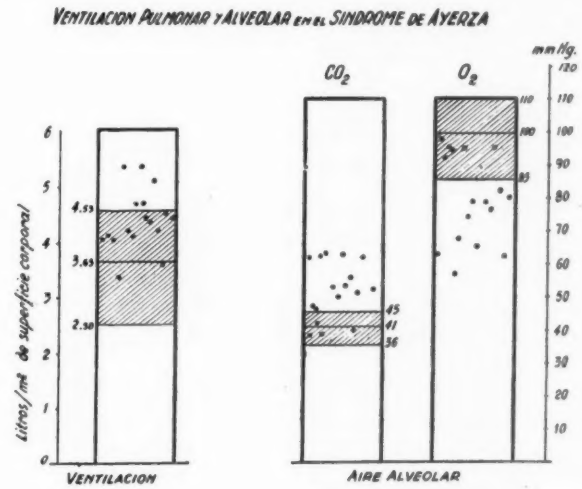

Fig. 2.—Pulmonary and alveolar ventilation. The points in each column represent the individual values found in the patients studied. The striped zone indicates the normal limits found in persons of more or less the same age. The central line represents the mean normal value.

of the residual air. Residual air values varied between 1 and 3.18 liters with a mean value of 2.27, which are above the normal figures. On the contrary, the reserve air, as well as the tidal air and the complemental air, was found diminished in most of the patients, the figures varying between 0.50 and 1.26 liters for the reserve air, 0.30 and 0.70 liter for the tidal air, and 0.90 and 2.77 liters for the complemental air. The modifications registered showed a marked increase in the relationship between the residual air and the total lung capacity in all patients except one.

Lung Ventilation.—In the patients studied there was an increase of the lung ventilation, the figures oscillating between 3.33 and 5.68 liters per minute and per square meter of body surface (Fig. 2). This increase was a consequence of the respiratory frequency, because, as we have already said, the tidal air was diminished in most of the patients.

Alveolar Air.—The study made of the alveolar air showed in most of the patients a marked diminution of the oxygen tension and an increase of the carbon dioxide tension. The highest and lowest figures for oxygen were 98.5 and 57.0 mm. Hg, respectively, and for carbon dioxide, 63.9 and 38.2 mm. Hg; the mean values were 85 for the first and 51.8 for the latter (Fig. 2). These quantities demonstrate that in most of these patients there existed a rather important diminution of the alveolar ventilation in spite of their increased lung ventilation.

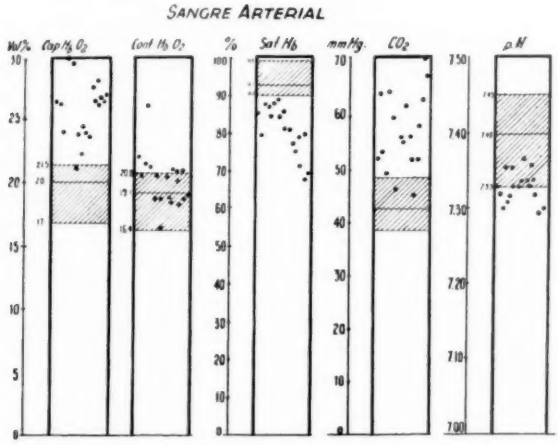

Fig. 3.—Hemoglobin, oxygen, carbon dioxide, and pH of the arterial blood. The points in each column represent the individual values found in the patients studied. The striped zone and the horizontal line drawn through the same represent the normal limits found in persons of more or less the same age and the mean normal value.

Arterial Blood (Fig. 3).—The study of the arterial blood of these patients showed an increase in the oxygen capacity that oscillated between 21.35 and 30 volumes per cent, as was to be expected from the polyglobulia and increase of hemoglobin mentioned before.

Oxygen and carbon dioxide tensions of the arterial blood showed figures ranging between 36 and 57.5 mm. Hg for the first tension and 46 and 67.2 for the second.

Together with the decrease of the oxygen tension in arterial blood a rather important degree of arterial unsaturation was found, hemoglobin figures in different patients being between 66.4 and 87.5 per cent. Although, as the blood's hemoglobin content was increased in most of the patients, the quantity of oxygen contained in arterial blood was slightly increased, the figures ranging between 17.86 and 22.24 per cent.

On the other hand, the carbon dioxide increases. Although almost compensated for by the increase of bicarbonate, pH of arterial blood showed in most of the patients a change to acidity, the figures found oscillating between 7.29 and 7.39, with a mean value of 7.33.

Discussion.—The group of patients studied from the respiratory standpoint showed (1) diminution of the respiratory efficiency, (2) alveolar hypoventilation, (3) increase of the oxygen capacity of the blood, and (4) marked unsaturation of the arterial blood with an increase of the carbon dioxide tension and a decrease of the pH.

The comparison of the oxygen tension both in the alveoli and in the arterial blood revealed a marked difference in our patients (Fig. 4). This difference, which has been observed by most investigators of the subject, is, as has been said, one of the reasons against the hypothesis that points to alveolar hypoventilation as the only cause for anoxemia.

There are at least three mechanisms which can explain the difference in the alveolar and arterial oxygen tension: (1) the existence of a disorder of diffusion that impedes the free passing of the oxygen through the alveolar wall to the blood;

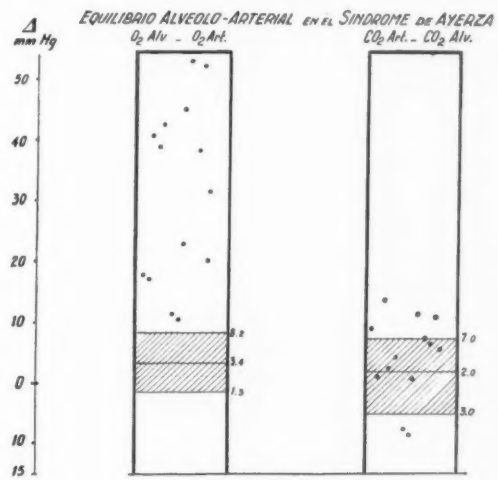

Fig. 4.—Alveolar-arterial equilibrium found in Ayerza's syndrome. Each point represents the equilibrium found in each individual case. The striped zone represents the normal limits found in normal persons of more or less the same age.

(2) the existence of arteriovenous shunts in the lung that permits some of the venous blood to pass through the lung without being converted into arterial blood; or (3) the irregular distribution of gases in the lungs which determines the existence of zones with different oxygen tensions.

As most of these patients had an increase of residual air and a diminished respiratory efficiency, it was thought at first that there was an irregular distribution of the gases in the lungs, a fact which has been proved in patients with emphysema.[5,7b,9,14,24,25 27,30] If this is what happens, the alveolar air, determined according to Haldane and Priestley's technique, would be the resultant of the combination of gases from different zones of the lung; each gas content would have a different composition and, therefore, the arterial blood would not be necessarily in equilibrium with alveolar oxygen (due to the presence of hemoglobin and the shape of its oxygen dissociation curve).

In order to study this problem three serial alveolar samples were taken, one after another, in the first six seconds of a deep expiration, the first one at 500 c.c., and the third one at 1,300 c.c., in those patients in whom expiration was large and rapid. In those patients in whom slow expiration prevented to obtain the aforementioned quantities within a period of six seconds, two samples were taken: one at 500 c.c., and the second, at the end of the mentioned period of time. Analysis was made of the samples thus obtained, and there were found to be noticeable differences in their composition in most of the patients (Table II).

The existence of this irregular distribution of the gas in the lung explains the increase in the difference between alveolar and blood O_2 tensions in most of the patients studied. This leads us to point out hypoventilation and uneven gas distribution as the causes of anoxemia in these persons. Notwithstanding, one patient (Case 10) showed normal oxygen and carbon dioxide tensions: 91 and 97 mm. Hg were the figures found for the oxygen tension and 40.8 and 38.2 mm. Hg for the carbon dioxide in duplicate determinations. Moreover, the serial alveolar air did not show significant abnormalities. From these facts we might conclude that in this patient there existed a satisfactory alveolar ventilation. Nevertheless, the arterial blood of this patient showed a high grade of anoxemia, since the oxygen tensions in the blood were only up to 45.2 and 43.5 in the two samples simultaneously analyzed, and so the alveolar-arterial oxygen difference is 45.8 and 53.5 mm. Hg, respectively. If it is true that even in this case it is possible to think that there existed certain deep zones of the lung in which the air was so inadequately renewed that those zones could not be reflected in the samples of alveolar air, we have also to take into consideration the probable existence of either a diffusion disorder irregularly distributed in the alveoli or arteriovenous shunts in the lung. These last hypotheses might be supported in this case by the facts that the patient (Case 10) had had a brief pulmonary clinical history; that the residual air was slightly augmented; and that post-mortem examination revealed predominately lesions of the arterioles and capillaries of the lung.

In summary it can be said that the studies made show that most patients with the Ayerza syndrome did not have a regular distribution of gases in the

lungs. The anoxemia that they presented on this basis is explained, although we will have also to consider as probable, in certain cases, the existence of a diffusion disturbance irregularly distributed or arteriovenous shunts as a consequence of chronic ailments of the lung.

TABLE II. SERIAL ALVEOLAR AIR TAKEN IN NORMAL PERSONS AND IN PATIENTS WITH AYERZA'S SYNDROME (DIFFERENCES IN TENSIONS OF OXYGEN AND CARBON DIOXIDE, FOUND IN SAMPLES TAKEN AT DIFFERENT TIMES DURING EXPIRATION, ARE FOUND TO BE MORE MARKED IN THE PATIENTS STUDIED THAN IN NORMAL PERSONS)

AYERZA'S SYNDROME

CASE	CO_2% ALVEOLAR			O_2% ALVEOLAR		
	SAMPLE 1	LAST SAMPLE	DIFFERENCE	SAMPLE 1	LAST SAMPLE	DIFFERENCE
D. F. 4	6.29 5.93	6.80 6.78	.51 .85	12.68 13.69	11.49 11.46	1.19 2.23
M. J. R. 5	5.91	6.68	.97	14.33	12.60	1.73
R. A. 7	6.37	8.80	2.43	12.13	7.58	4.55
D. Fe. 13	6.20 6.47	6.97 6.63	.77 .16	12.80 12.54	11.43 11.37	1.37 1.17
C. S. 15	8.16	8.72	.56	11.38	9.97	1.41
Average			.99			2.13

NORMAL SUBJECTS

SUBJECT	CO_2% ALVEOLAR			O_2% ALVEOLAR		
	SAMPLE 1	LAST SAMPLE	DIFFERENCE	SAMPLE 1	LAST SAMPLE	DIFFERENCE
M. V	5.69 6.17	6.20 6.41	.51 .24	14.00 14.82	13.69 14.07	.31 .75
L. C. F.	4.55 4.42	5.05 4.44	.50 .02	16.34 16.89	15.61 16.84	.73 .05
J. R. S.	5.86 5.65	6.25 5.87	.39 .22	12.31 13.11	11.16 13.11	1.15 0.00
M. Ch.	5.68 5.52	5.84 5.80	.16 .28	13.30 14.19	12.58 13.78	.72 .41
A. M.	3.46 3.63	3.86 3.94	.40 .31	17.08 16.74	16.25 16.00	.83 .74
Average			.30			.57

The presence or absence of cyanosis and the degree of the same in these patients can be explained by the degree of oxygen unsaturation as well as the increase in hemoglobin observed in almost all of them (Fig. 5).

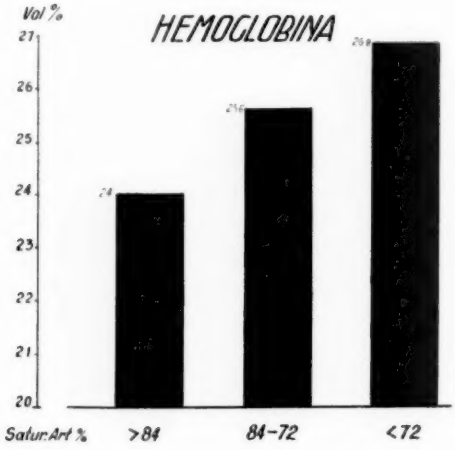

Fig. 5.—Hemoglobin amount in relation to anoxemia. Each column represents the average value of hemoglobin (in volume per cent) in each of the groups in which the patients were classified according to the degree of arterial saturation.

CIRCULATORY FUNCTION

Blood Volume.—In the ten patients studied, the total blood volume oscillated between 5.21 and 11.95 liters; these quantities corresponded to 72.4 to 163.7 c.c. per kilogram of body weight (Fig. 6). These figures coincided with normal standards in only two of the ten patients studied; they were markedly higher than normal in the remaining eight. The increase in the blood volume varied from 12 to 121 per cent. Since some of our patients presented cardiac failure, with noticeable edema, the figure of volume per meter of height was taken as a comparative index, in relation to our standards. When these calculations were made, all the patients studied showed an increase of the blood volume, which varied from 13.5 to 142 per cent, with an average increase in the ten patients of 55.3 per cent. The plasma volume varied from 2.28 to 3.08 liters, which corresponded to 32.5 and 53.1 c.c. per kilogram of body weight. In three patients the plasma volume was found to be within normal limits, in five there was a moderate diminution, and in two a moderate increase was observed; the whole group deviation was +3.98 per cent.

The erythrocyte volume varied between 2.93 and 9.02 liters, which corresponded to 36.9 and 125.5 c.c. per kilogram of body weight. In all the patients there was an increase of the erythrocyte volume that varied from 9 to 241.1 per cent.

These results show that in our patients with Ayerza's disease there exists an increase of the blood volume due to an increase of the red cells. The plasma volume, on the contrary, was found to be practically normal because the varia-

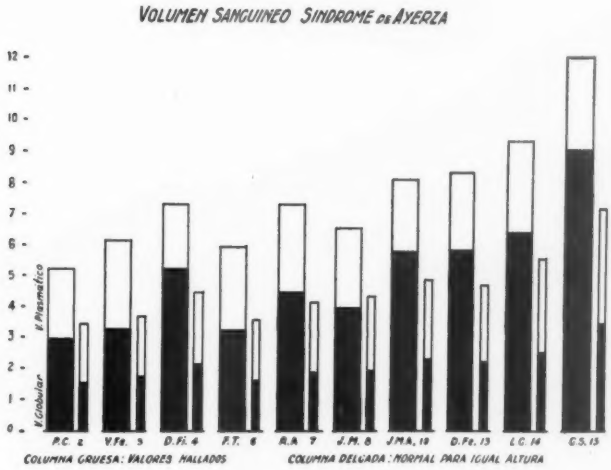

Fig. 6.—Blood volume found in Ayerza patients. The thick columns represent the figures found in the different cases. The thin columns represent the normal values of persons of similar heights.

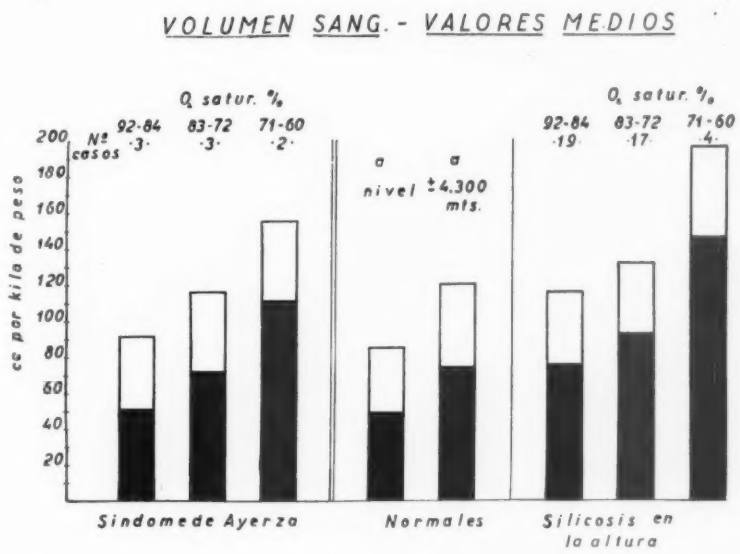

Fig. 7.—Average blood volume found in each group of patients with Ayerza's syndrome, with different degrees of arterial saturation, compared with the values found by Hurtado and associates in normal persons and in patients with silicosis.

tions registered were very small and the existence of edema as well as the undernourishment of some patients made possible the presence of errors in the calculation of the plasma volume per kilogram of body weight. Since the most marked increases of the blood volume coincided with the lowest figures of oxygen saturation in the blood, it is logical to accept the fact that the increase of the erythrocyte volume is provoked by the stimulation of the bone marrow by anoxemia.

The existence of a relation between both factors was clearly shown when the patients were divided into three groups with blood saturations between 84 and 92 per cent for the first group, 72 and 84 per cent for the second, and 61 and 72 per cent for the third group (Fig. 7). The individual variations registered can be explained by factors such as sex, the patient's condition, intercurrent infections, and recent variations in the oxygenation of the blood. Nevertheless, it must be admitted that there are personal variations, because even normal persons give different marrow responses to different grades of anoxemia, as has been pointed out by Hurtado, Merino, and Delgado.[16]

Since the highest blood volumes were found in patients suffering from cardiac failure, it might be possible that such an ailment contributed to the increase of the blood volume, although we can not be sure that cardiac failure was one of the causes of hypervolemia in our patients, because the patients suffering from it were those with the highest degrees of anoxemia.

Venous Pressure.—The results show that the venous pressure was markedly elevated in only four patients, and these patients had cardiac failure (Fig. 8).

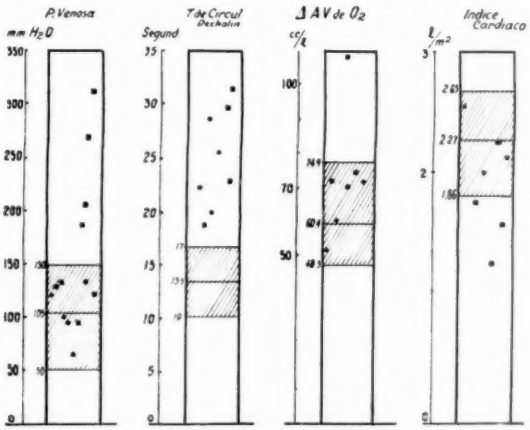

Fig. 8.—Venous pressure, circulation time, arteriovenous oxygen difference, and cardiac index in patients with Ayerza's syndrome. In circles and squares are shown the individual values found in patients with and without cardiac failure, respectively. The striped zones represent the normal limits.

These results coincide with those of Oppenheimer and Hitzig[21] and of Kaltreider.[18] Although, from the analysis of a large number of patients, it has been concluded that in those with advanced emphysema and with noticeable

variations of the pleural pressure, the venous pressure has a tendency to be elevated in the absence of cardiac failure.[19,22] This increase may reach the maximum normal limits and even surpass them (personal data).

Circulation Time.—Decholin time was greater than 20 seconds in all the patients but one. Ether time was normal in only one patient; in all the other patients it was prolonged. As was expected, the most prolonged circulation times were found in those patients with cardiac failure. No relation was noted between the venous pressure and the circulation time. Our results coincide with those obtained by Jimenez Diaz, Agesta, and Alemany.[17] They do not agree, however, with those found by Weiss and Blumgart,[31] or by Oppenheimer and Hitzig[21] in patients with pulmonary fibrosis and emphysema. These slight variations have no particular significance because our study has been made on a special group of patients with marked polycythemia and variations of the blood volume, which explain the delay found in the circulation time.

Cardiac Output.—This was studied in seven patients in whom the amplitude of the vital capacity, as well as the conditions of the respiratory mechanisms, permitted the use of Grollman's four-sample method with probabilities of success.

The results given in Fig. 8 show that in the patients who had only respiratory insufficiency, the cardiac output was within normal limits despite the existence of pulmonary alteration, anoxemia, or polycythemia. These results coincide with those found by Ayerza, Solari, and Berconsky[3] and by Arrillaga, Berconsky, and Taquini[2] which proved that the minute output is normal in patients with the Ayerza's syndrome without cardiac failure. On the contrary, in those patients with cardiac insufficiency the minute output showed rather diminished values. This fact suggests a direct relation between the heart's functional capacity and the cardiac output; this relation is similar to that found in other heart diseases studied by Suarez, Fasciolo, and Taquini.[28] This might also be the cause of the diminution of the cardiac output found in the cases studied by Cossio and Berconsky,[8] by Berconsky,[4] and by Capdehourat.[6]

Discussion.—These results show that patients with Ayerza's syndrome have a normal cardiac output, a marked increase of the blood volume, an increase of the circulation time, and a normal or slightly modified venous pressure. The heart would have to increase its work very much in order to maintain a normal minute output, because there is a marked increase in the blood's viscosity caused by the polyglobulia. Since this did not happen in our patients, because the arterial pressure did not rise in every case, we have to admit that there exists a mechanism of adaptation. The permanent dilatation of the arterial and capillary bed is immediately suggested as the obvious explanation. This hypothesis is supported by the fact that the increase of the blood volume as well as that of the erythrocytes and the hemoglobin was in relation to the anoxemia. This adaptation would permit a great diminution of the blood's velocity without modifying the minute output and the arteriovenous difference[1] (Fig. 9). This is the reason why, in our patients, the time needed by the blood to complete its circuit (time is calculated by dividing the minute output by the blood volume)

was almost twice as long as the time needed in normal persons. In spite of this, the arteriovenous difference was normal, thus showing that the blood flow in the unit of time was normal. The diminution of the blood's velocity, determined by the increase of the vascular bed and the blood volume, would permit the maintenance of the heart's volume output without increasing the peripheral resistance; that is, without increasing the heart's work. This circulatory equilibrium is one of the most interesting known mechanisms of adaptation; it explains how these patients can tolerate the disorders produced by the hyperglobulia without much inconvenience.

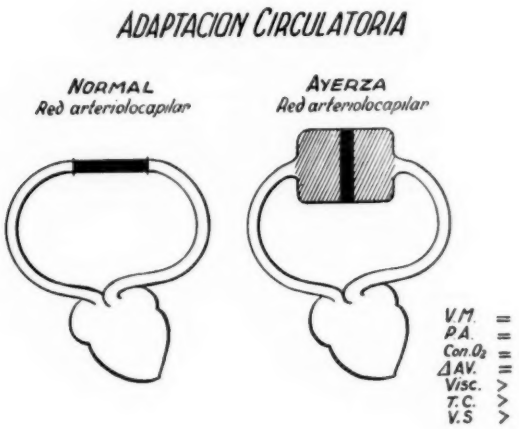

Fig. 9.—Diagram representing the circulatory adaptation in Ayerza's disease. It is noticeable that the greater the vascular bed and the blood volume, the less the velocity necessary to maintain a normal blood flow.

On the other hand, the increase of the hemoglobin's capacity has an important role in order to maintain a normal quantity of oxygen carried by the blood despite the existence of the unsaturation. This adaptation of the blood to anoxemia and the previously mentioned circulatory adaptations almost compensate for the changes in the arterial blood caused by the alveolar hypoventilation. As a result, the O_2 pressure of the venous blood is very near normal values; the state of the venous blood can be considered to show the changes going on in the tissues (Table III).

All these facts explain why patients with Ayerza's syndrome are able to maintain a rather normal function of their organs in spite of the existence of such accentuated arterial anoxemia. It also explains why their hearts maintain their functions without any further clinical signs of myocardial anoxemia; and why these patients develop mostly right heart insufficiency as a result of hemodynamic alterations provoked by pulmonary ailments.

TABLE III. OXYGEN AND CARBON DIOXIDE PRESSURES AS WELL AS pH OF ARTERIAL AND VENOUS BLOOD FROM PATIENTS WITH AYERZA'S SYNDROME COMPARED WITH MEAN NORMAL VALUES

	ARTERIAL BLOOD			MIXED VENOUS BLOOD		
		AYERZA'S SYNDROME			AYERZA'S SYNDROME	
	NORMALS	WITHOUT CARDIAC INSUFFICIENCY	WITH CARDIAC INSUFFICIENCY	NORMALS	WITHOUT CARDIAC INSUFFICIENCY	WITH CARDIAC INSUFFICIENCY
pO_2 mm. Hg	95	48.7	47.7	35	31.7	28.0
pCO_2 mm. Hg	41	55.4	53	49	60.5	62
pH	7.40	7.34	7.33	7.36	7.32	7.31

CONCLUSIONS

1. Studies made on sixteen patients with Ayerza's syndrome have enabled us to demonstrate the existence of the following alterations in all patients: (a) alveolar hypoventilation, (b) diminution of oxygen tension in the arterial blood, (c) increase of the carbon dioxide tension, (d) diminution of pH, (e) hemoglobin increase, (f) increase of blood volume, and (g) increase of the circulation time.

Arterial blood pressure, cardiac output, and arteriovenous oxygen difference showed no change directly attributable to the hemo-respiratory alterations.

2. Alveolar hypoventilation, as well as inadequate distribution of the gases in the lungs, easily explains the anoxemia observed in most of the patients studied.

3. Anoxemia was also fundamental in producing hemoglobin and blood volume increase.

4. Increase of hemoglobin held the amount of oxygen in the blood in quantities near normal, even though a marked decrease of oxygen tension existed.

5. Although blood velocity was decreased, an increase in blood volume permitted normal arteriovenous difference and cardiac output.

6. Decrease in blood velocity and increase in the volume of the vascular bed in patients with Ayerza's syndrome explains how the heart can maintain normal minute output and arterial blood pressure within normal limits in spite of the presence of a marked increase in the viscosity of the blood.

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EFFECTS OF INTRAVENOUS INJECTION OF NICOTINE ON THE CIRCULATION

In Normal Persons and in Patients With Cardiovascular Disease

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THERE is ample evidence that the important ingredient of tobacco smoke, with respect to its action on the cardiovascular system, is nicotine.[1] Other toxic constituents, such as the pyridine bases, hydrocyanic acid, and ammonia, are present in amounts so small that they exert no appreciable effects. The concentration of carbon monoxide in the blood after smoking, except in extreme instances, does not reach sufficiently high levels to embarrass the circulation at ordinary altitudes.[2] By observing the effects of nicotine after intravenous injection, any possible action of these other substances is eliminated and no factors are present which might induce reflex disturbances, such as irritation of the mucous membranes or the act of inhalation. The results of such a study cannot be translated into terms directly applicable to the smoking of tobacco, but they furnish information concerning the immediate response of the heart and circulation to the most active substance absorbed from the smoke.

MATERIAL, PROCEDURE, AND METHODS

Clinical Material (Table I).—Observations were made on forty-six subjects. Of these, eighteen were normal persons ranging in age from 22 to 74 years; the average was 32.7 years. Eleven were smokers and seven were nonsmokers. There were twenty-four patients with coronary heart disease. Of these, twenty suffered from attacks of anginal pain and ten had hypertension, and in four a healed myocardial infarct was known to be present. The ages ranged from 40 to 78 years, with an average of 55.9 years. Seventeen were smokers and seven were nonsmokers. There were four patients with peripheral vascular disease. The diagnosis was Raynaud's disease in two, thromboangiitis obliterans in one, and scleroderma with gangrene of the fingers in one. The ages ranged from 21 to 50 years, with an average of 39.5 years. Three were smokers and one was a nonsmoker.

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To these forty-six individuals, sixty-four intravenous injections of nicotine were given.

TABLE I. SUMMARY OF CLINICAL MATERIAL

Number of subjects			46
Number of nicotine injections			64
Determinations of cardiac output			18
Normals			18
Smokers		11	
Nonsmokers		7	
Ages, 22 to 74; average, 32.7 years			
Coronary heart disease			24
With anginal pain	20		
With hypertension	10		
With healed infarction	4		
Smokers		17	
Nonsmokers		7	
Ages, 40 to 78; average, 55.9 years			
Peripheral vasular disease			4
Raynaud's disease	2		
Thromboangiitis obliterans	1		
Scleroderma	1		
Smokers		3	
Nonsmoker		1	
Ages, 21 to 50; average, 39.5 years			

Preparation and Dosage.—The preparation employed was nicotine bitartrate.* It was preferred to other salts because of its ready solubility in water and its stability. The bitartrate contains 32.54 per cent of nitocine, 60.23 per cent of tartaric acid, and 7.23 per cent of water.[3]

The dosage used was 2 mg. dissolved in 2 c.c. of water. The amount of alkaloid contained in 2 mg. of bitartrate is approximately 0.6 milligram. This was injected intravenously, after mixing it with blood in the barrel of the syringe. Tests indicated that such admixture did not lessen the potency of the alkaloid. The effects of the injection of 0.5 mg. in a dog are shown in Fig. 1. This dose is about 20 per cent larger (milligrams per kilogram of body weight) than that given to the human subjects. The increase in blood pressure and heart rate, as well as the acceleration in respiration, are clearly seen.

Procedure.—All observations were made with the patients in the recumbent position. The needle was inserted into the vein several minutes before the injection was given. Repeated recordings were made of the heart rate and of the systolic and diastolic blood pressures. The cardiac output was determined by means of the ballistocardiograph devised by Nickerson and Curtis.[4] According to this technique, a change of 10 per cent may be considered significant. Determinations of the blood sugar were made by the method of Folin,[5] with the subjects in the fasting state.

Two control electrocardiograms were made and records were taken at frequent intervals after the injection of nicotine. In addition to the usual limb

*Nicotine bitartrate in aqueous solution was supplied in ampoules by the Abbott Laboratories, North Chicago, Ill., through the courtesy of Dr. J. F. Biehn, Director of the Department of Medicine.

leads, precordial Lead IV F was taken. Changes were regarded as "slight" if there was (1) decrease in the amplitude of the T wave, in any lead, of 1 mm. or more, or (2) deviation of the RS-T segment, in any lead, of less than 1 millimeter. Changes were considered "significant" if there was (1) complete or partial reversal in the direction of T_1, T_2, or T_4F, or (2) deviation of the RS-T segment, in any lead, of 1 mm. or more.

Any symptoms of which the patient complained were noted.

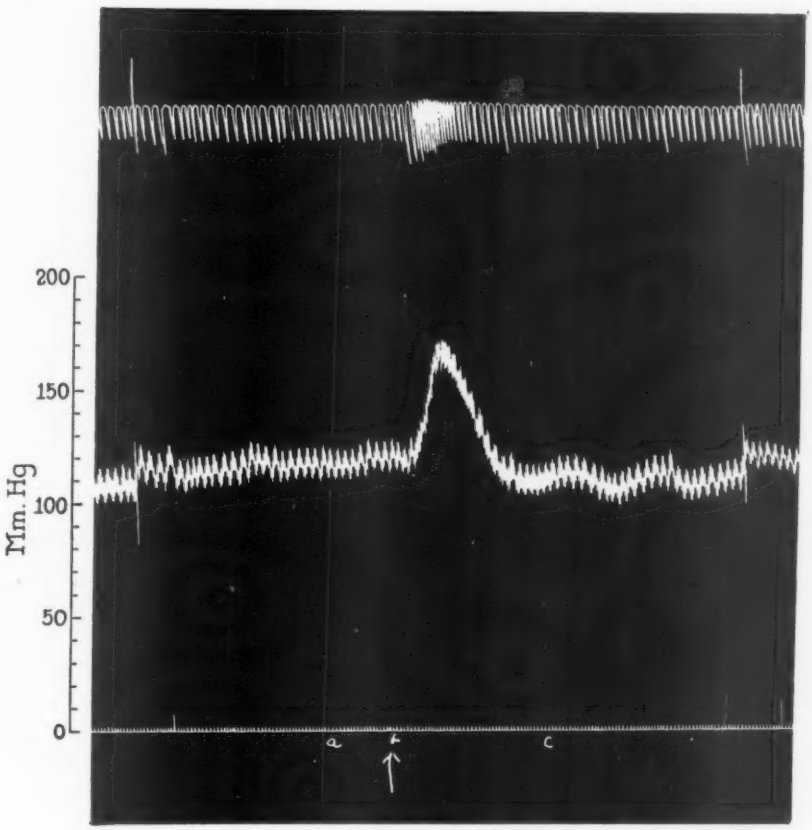

Fig. 1.—Dog, weight 14.5 kilograms. Anesthesia induced by morphine, followed by 1.5 c.c. per kilogram of 20 per cent sodium barbital, injected intravenously. Upper tracing, respiration. Lower tracing, blood pressure. Time, in seconds. At *b*, intravenous injection of 0.5 mg. nicotine bitartrate.

RESULTS

The results were tabulated for the three groups of individuals studied (Table II). In each group a further subdivision was made into smokers and non-smokers. The analysis was designed to indicate the degree of change which occurred in the indexes employed and to make possible a comparison of the effects in the three groups of cases. The statistical significance of the averages was determined by comparing them with their standard error; this depends upon the number of readings and their range of variation.

In all of the analyses no significant differences were observed between smokers and nonsmokers, so that in the discussion which follows these categories have been combined.

Heart Rate (Table II).—The average change in heart rate in normal individuals was +19 beats per minute; the range was from 0 to +57. The average change in the patients with coronary heart disease was +14; the range was from −12 to +42. In those with peripheral vascular disease, the average change was +12; the range was from +8 to +28. There were no significant differences in the averages of the three groups.

TABLE II. AVERAGES OF THE MAXIMAL CHANGES OBSERVED IN HEART RATE, BLOOD PRESSURE AND CARDIAC OUTPUT IN THREE GROUPS OF INDIVIDUALS AFTER INTRAVENOUS INJECTION OF 2 MG. NICOTINE BITARTRATE

	NORMALS		CORONARY HEART DISEASE		PERIPHERAL VASCULAR DISEASE	
	NUMBER CASES	AVERAGE	NUMBER CASES	AVERAGE	NUMBER CASES	AVERAGE
Heart Rate (Beats per minute)						
Smokers	11	21	17	15		
Nonsmokers	7	16	7	11		
Totals	18	19	24	14	4	12
Systolic Blood Pressure (mm. Hg)						
Smokers	11	10	17	12		
Nonsmokers	7	11	7	20		
Totals	18	10	24	15	4	16
Diastolic Blood Pressure (mm. Hg)						
Smokers	11	6	17	7		
Nonsmokers	7	10	7	13		
Totals	18	8	24	9	4	8
Cardiac Output (liters per minute), Smokers and Nonsmokers						
Totals	8	1.9	7	0.8	3	1

Systolic Blood Pressure (Table II).—In the normal subjects the average change was +10 mm. Hg; the range was from +2 to +22. In the patients with coronary heart disease, the average change was +15; the range was from +4 to +60. In those with peripheral vascular disease, the average change was +16; the range was from +2 to +50. There were no significant differences in the averages of the three groups.

Diastolic Blood Pressure (Table II).—In the normal subjects the average change was +8 mm. Hg; the range was from 0 to +20. In the patients with coronary heart disease, the average change was +9; the range was from −2 to +25. In those with peripheral vascular disease, the average change was +8; the range was from 0 to +20. There were no significant differences in the averages of the three groups.

Cardiac Output (Table II).—In the normal group the average change was +1.9 liters per minute; the range was from −0.4 to +7.5. There was a significant rise in six subjects and a slight fall in two. In the patients with coronary heart disease, the average change was +0.8; the range was from −1.9 to +2.3. There was a significant rise in five patients and a slight fall in two. In those with peripheral vascular disease, the average change was +1.0; the range was from +0.2 to +1.8. There was a significant rise in three patients; in the fourth patient no determinations of output were made. There were no significant differences in the averages of the three groups.

Electrocardiogram.—Electrocardiograms were taken in sixteen of the normal individuals. There was no change in nine, a slight change in seven, and a significant change in none. In the patients with coronary heart disease, there was no change in eighteen, a slight change in three, and a significant change in three. In those with peripheral vascular disease, there was no change in two, a slight change in one, and a significant change in one. The patient in this latter group whose electrocardiogram showed a significant change was a woman 47 years of age with scleroderma and ulceration of the fingers, in whom coronary heart disease was also present. The anoxemia test in this patient was positive. In two of the patients showing significant changes, the control electrocardiogram was abnormal; in two it was normal.

Symptoms.—Symptoms occurred in thirteen normal subjects, sixteen patients with coronary heart disease, and three with peripheral vascular disease. There was great individual variation in their number and severity. Immediately after the injection was completed, almost every subject took several deep breaths. In all groups, the commonest complaint was dizziness. Other sensations were tingling and faintness. Nausea occurred three times. Anginal pain occurred in two of the patients in the coronary group in whom significant alterations in the electrocardiogram were observed.

One unusually severe reaction was encountered. This occurred in a normal man, 24 years of age. He had never smoked but could give no particular reason for not having done so. The control heart rate was 64 per minute; the blood pressure was 105/85. After intravenous injection of the usual dose of nicotine,

he perspired profusely and became pale and cold. In a few minutes he was nauseated and vomited. The pulse became thready and the blood pressure, for a short time, was not obtainable. He then retched for five minutes, felt nauseated for an hour, and was weak for the remainder of the morning. Because of the violence of the reaction, electrocardiograms were not taken and the cardiac output could not be determined. His record, therefore, is not included in the series.

Blood Sugar.—Eight determinations were made in seven subjects, of whom three were normal and four were patients with coronary and hypertensive heart disease (Table III). A control sample was taken, and blood was drawn three and ten minutes after the injection of nicotine. No consistent variations were found, although there were some fluctuations, both upward and downward, which were greater than the error inherent in the method. In one patient, P., the control reading on one occasion was 111 mg. per cent; three minutes after nicotine injection, the level rose to 133, an increase of almost 20 per cent. On another occasion, the control reading in the same patient was 86; ten minutes after nicotine injection, the level fell to 68, a decrease of 20 per cent. In none of the subjects was there an apparent correlation between the direction or degree of change in the blood sugar level and variations in blood pressure, heart rate, or the form of the electrocardiogram.

DISCUSSION

Careful studies of the nicotine content of tobacco smoke have been made by Baumberger.[6] He found that the amount of nicotine in the puffed smoke of one cigarette is about 4.5 milligrams. Four cigarettes are equivalent to one mild cigar. The frequency of puffing determines the rate of absorption.

Approximately 66.7 per cent of the smoke and, presumably, the nicotine drawn into the mouth, are absorbed. If the smoke is inhaled, 88.2 per cent are absorbed. Assuming 66.7 per cent absorption and a rate of puffing of five per minute, the dosage rate of nicotine from cigarette smoke would be 0.46 mg. per minute, or 27.5 mg. per hour. With inhalation, and hence absorption of 88.2 per cent, the dosage rate would be 0.6 mg. per minute, or 36 mg. per hour.

On the basis of these figures, about 3 mg. of nicotine are absorbed from a cigarette if not inhaled, and 4 mg. if the smoke is drawn into the lungs. It has already been mentioned that 2 mg. of the bitartrate, which was the amount injected in each subject, contain 0.6 mg. of nicotine alkaloid. The dose employed, therefore, was relatively small. But it was introduced directly and quickly into the circulation and was large enough to cause reactions which were readily measurable.

The most striking feature apparent from our results is the marked individual variation in response observed in members of all groups studied. Examples are given in the following brief clinical notes and are illustrated.

CASE 1.—D. P. was a normal woman, 24 years of age, who never inhaled and limited herself to two cigarettes a week because smoking caused palpitation and heartburn. After injection of nicotine, there was a sharp rise in blood pressure, heart rate, and cardiac output (Fig. 2). The

TABLE III. EFFECT OF INTRAVENOUS INJECTION OF 2 MG. NICOTINE BITARTRATE ON BLOOD SUGAR IN RELATION TO CHANGES IN THE CIRCULATION

SUBJECT	DIAGNOSIS	BLOOD SUGAR (MG. PER CENT)				MAXIMAL CIRCULATORY CHANGES			ELECTROCARDIOGRAPHIC CHANGES	
		CONTROL	3 MIN.	10 MIN.	MAXIMAL CHANGE	SYSTOLIC BLOOD PRESSURE (MM. HG)	DIASTOLIC BLOOD PRESSURE (MM. HG)	HEART RATE (BEATS PER MIN.)	SLIGHT	SIGNIFICANT
D.	Normal	114	103	101	−13	+10	+10	+12	0	0
Ca.	Normal	83	85	74	+2:−9	+15	+20	+2	0	0
K.*	Normal	88	93	87	+5:−1	+15	+12	+48	+	−
M.	Coronary heart disease	124	121	120	−4	+10	+2	+8	0	0
E.	Coronary and hypertensive heart disease	78	89	77	+11:−1	+18	+10	+20	−	+
Ch.	Hypertensive heart disease; syphilitic aortitis	133	118	123	−15	+10	+8	+16	0	0
P.	Coronary and hypertensive heart disease; healed cardiac infarct	111	133	117	+22	+4	0	+4	0	0
		86	79	68	−18	+10	+8	+8	0	0

*Received only 1 mg. nicotine because of sharp reaction in previous tests.

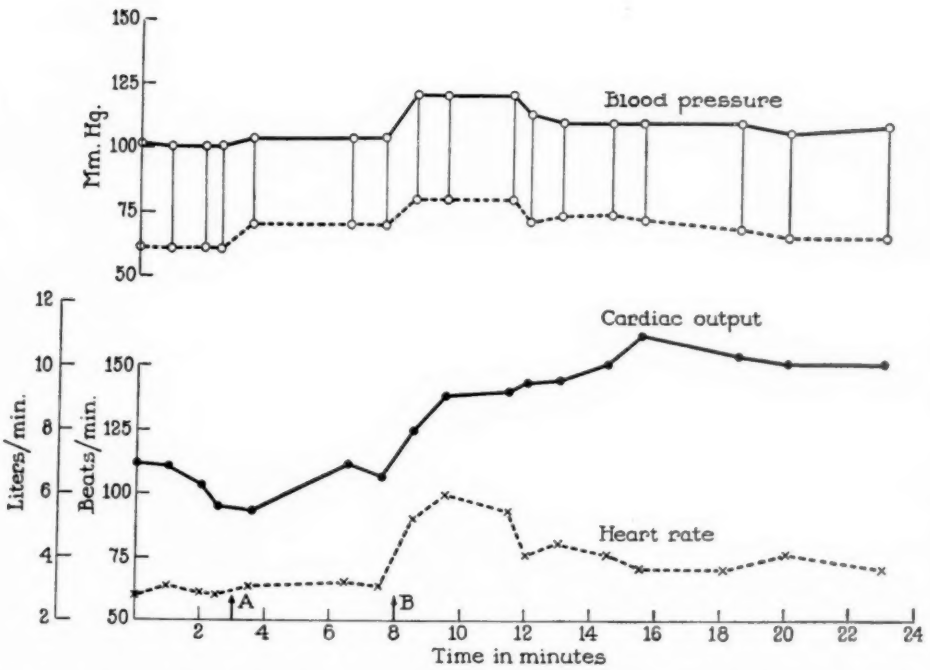

Fig. 2.—Case 1. Normal woman, 24 years of age. At *A*, needle injected into vein. At *B*, 2 mg. nicotine bitartrate injected. Became dizzy and faint.

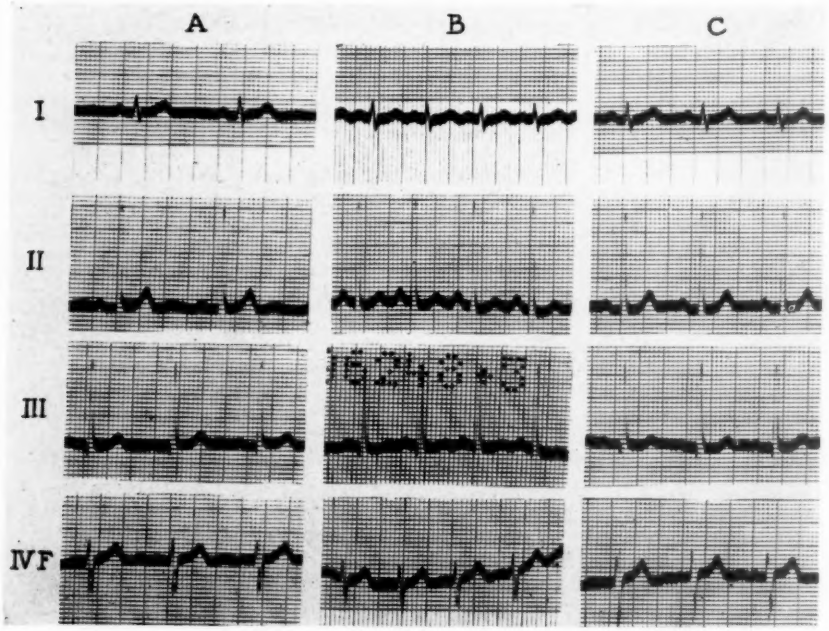

Fig. 3.—Case 1. Normal woman, 24 years of age. *A*, Control. Needle in vein. Rate, 88; blood pressure 110/65. *B*, One minute after injection of 2 mg. nicotine bitartrate. Rate, 136; blood pressure 130/85. Became dizzy and faint. *C*, Nine minutes after injection. Rate 98; blood pressure, 115/65.

increase in cardiac output was sustained throughout the period of observation. She complained of dizziness and faintness.

The control electrocardiogram was normal. After nicotine injection, it showed tachycardia, lowering of the T waves in all leads, and depression of the RS-T segments in Leads I, II, and III (Fig. 3). The changes in form were slight.

CASE 2.—R. D. was a normal man, 26 years of age, who had smoked twenty cigarettes daily for eight years and always inhaled. The control electrocardiogram was normal. After nicotine injection (Fig. 4) there was a slight and very transitory rise in blood pressure. The heart rate increased a few beats. The cardiac output fell. There were no symptoms. The electrocardiogram showed no changes. Injection of 4 mg. of nicotine bitartrate caused no greater effects.

CASE 3.—H. E. was a woman, 66 years of age, with coronary and hypertensive heart disease who had been subject to attacks of anginal pain for seven years. She had never smoked. The control electrocardiogram showed regular sinus rhythm. The T waves in the limb leads were of low amplitude but were upright. There was sharp inversion of T_4F and slight depression of the RS-T segments in Leads I, II, and IV F.

Several minutes after the injection of nicotine, she experienced severe precordial pain which radiated down the left arm. This increased in severity and continued for eight minutes, when nitroglycerin was given and afforded immediate relief. The changes in the electrocardiogram were accentuated in that T_1 became diphasic and the depressions of RS-T, particularly in Lead IV F, became more marked. The total increase in RS-T depression measured 3.5 millimeters. Twelve days later the same dose of nicotine caused the heart rate to rise from 80 to 110 beats per minute and the blood pressure, from 150/90 to 156/106. The cardiac output increased from 5.1 to 7.4 liters per minute (Fig. 5). There was slight precordial pain, but this symptom required no medication. The same changes were observed in the electrocardiograms.

Three months later the patient was having fewer anginal attacks, having spent the early weeks of the intervening period in the hospital and the latter part in a convalescent home. After nicotine injection, the heart rate rose from 84 to 100 beats per minute and the blood pressure, from 128/78 to 144/88. No pain was felt. The form of the control electrocardiogram was as previously described and nicotine caused the same changes.

CASE 4.—B. C. was a man, 53 years of age, with coronary and hypertensive heart disease. He had suffered from attacks of anginal pain for three years, and one year previously had been in the hospital because of cardiac insufficiency. He had smoked twenty cigarettes daily and an occasional cigar for years, but for two months had cut down to two cigars daily.

The control electrocardiogram showed regular sinus rhythm with an occasional ventricular premature beat. Left axis deviation was marked. The T wave was inverted in Lead I, upright in Leads II and III, and diphasic in Lead IV F. He had been taking maintenance doses of digitalis for some time, and some of these alterations may have been due to the action of this drug.

Nicotine injection caused no change in heart rate and a slight rise in systolic blood pressure. The cardiac output was decreased (Fig. 6). The electrocardiogram was unchanged.

Observations on the effects of smoking and of nicotine injection on the circulation have recently been reported by Roth, McDonald, and Sheard[7]; they also reviewed earlier work. The electrocardiograms of normal persons have shown lowering of the T waves,[8] and sometimes inversion in Leads II and III.[9] Of particular interest are two cases of coronary heart disease described by Wilson and Johnston.[10] In both patients, after smoking one or two cigarettes, changes occurred in the electrocardiogram resembling those seen in the early stages of infarction of the posterior wall of the heart. Because of the lack of parallelism between the magnitude of the changes and cardiac work, as represented by increase in heart rate and blood pressure, Wilson and Johnston concluded that nicotine or some other ingredient of tobacco smoke sometimes induces coronary

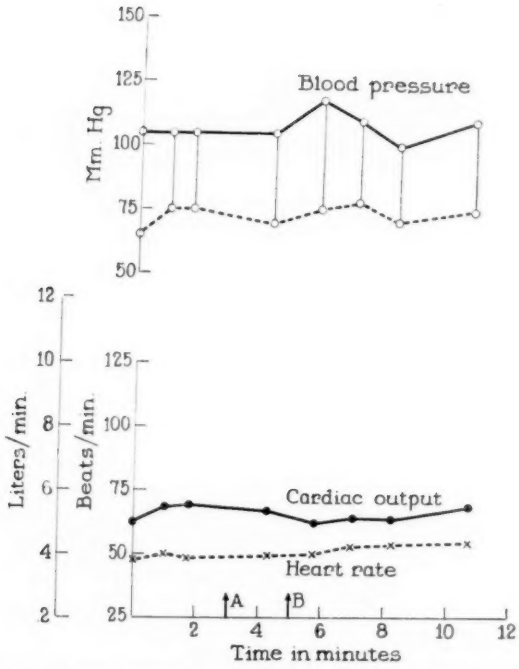

Fig. 4.—Case 2. Normal man, 26 years of age. At *A*, needle inserted into vein. At *B*, 2 mg. nicotine bitartrate injected. No discomfort.

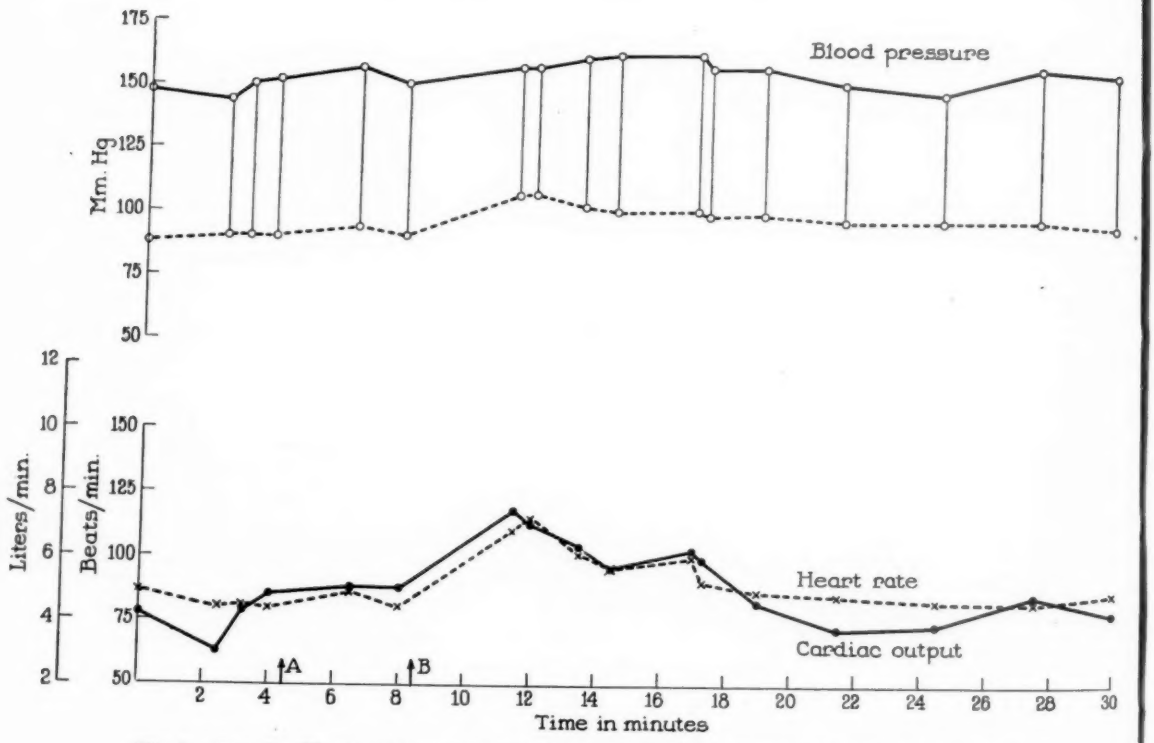

Fig. 5.—Case 3. Woman, 66 years of age, with coronary heart disease and anginal pain. At *A*, needle inserted into vein. At *B*, 2 mg. nicotine bitartrate injected. Complained of precordial pain, which was relieved by nitroglycerine.

spasm in patients subject to anginal attacks. Graybiel and collaborators[9] and Pickering and Sanderson,[11] on the other hand, were inclined to ascribe cardiac pain induced by smoking to the increased work of the heart rather than to constriction of the coronary arteries.

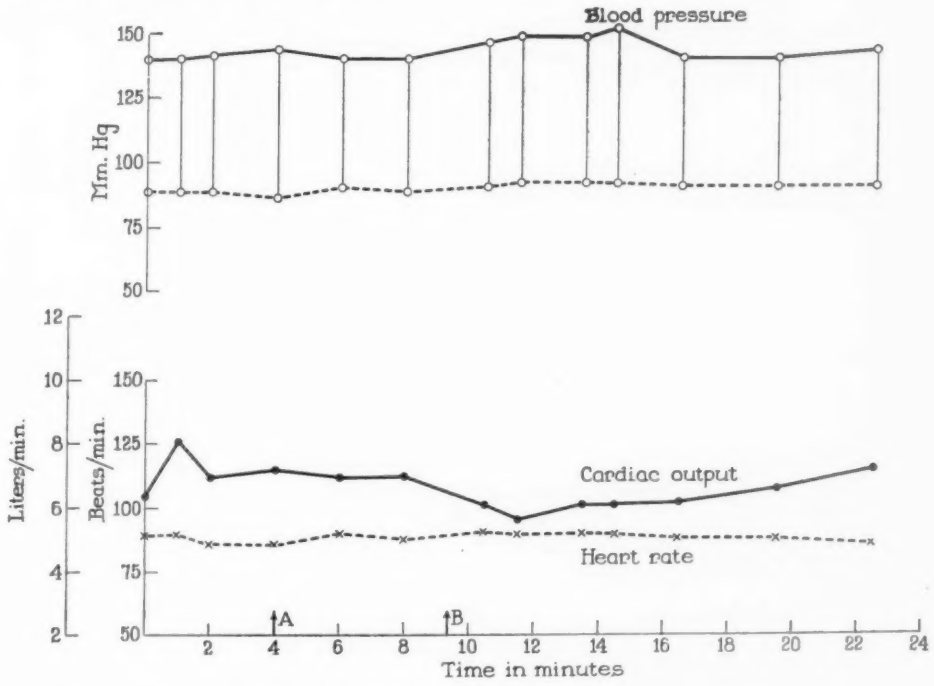

Fig. 6.—Case 4. Man, 53 years of age, with hypertensive cardiovascular disease and anginal pain. At *A*, needle inserted into vein. At *B*, 2 mg. nicotine bitartrate injected. No pain.

Significant alterations in the form of the electrocardiogram after nicotine injection were observed in four of our patients with coronary heart disease. Three of them were subject to anginal attacks; in only two, however, did pain accompany the electrocardiographic changes. The man (G. M.) whose tracings are shown in Fig. 7 was treated at the hospital for posterior cardiac infarction three months before these observations were made. Fifteen minutes after nicotine injection, the increase in heart rate was twelve beats per minute; the systolic blood pressure rose only 8 mm. Hg and the diastolic, 2 millimeters. He did not experience pain. Yet the changes in the electrocardiogram were well defined, with depression of the RS-T segments in Leads I, II, and IVF and partial inversion of the T waves in the precordial lead. These changes were similar to the ones caused by induced anoxemia in patients with coronary insufficiency.[12]

In one other patient with significant electrocardiographic changes, the increase in heart rate was slight. In a third patient the rise in systolic blood pressure was only 4 mm. Hg, and in diastolic, 12, but the heart rate rose thirty beats and the cardiac output increased 2.3 liters per minute. Only in patient

G. M. were the increases in both heart rate and blood pressure so small that they hardly could be credited with augmenting cardiac work to a degree corresponding to the changes in the electrocardiogram. It seems reasonable to infer, therefore, that nicotine may induce coronary insufficiency by constricting the coronary arteries or by increasing the work of the heart. Probably both mechanisms are concerned.

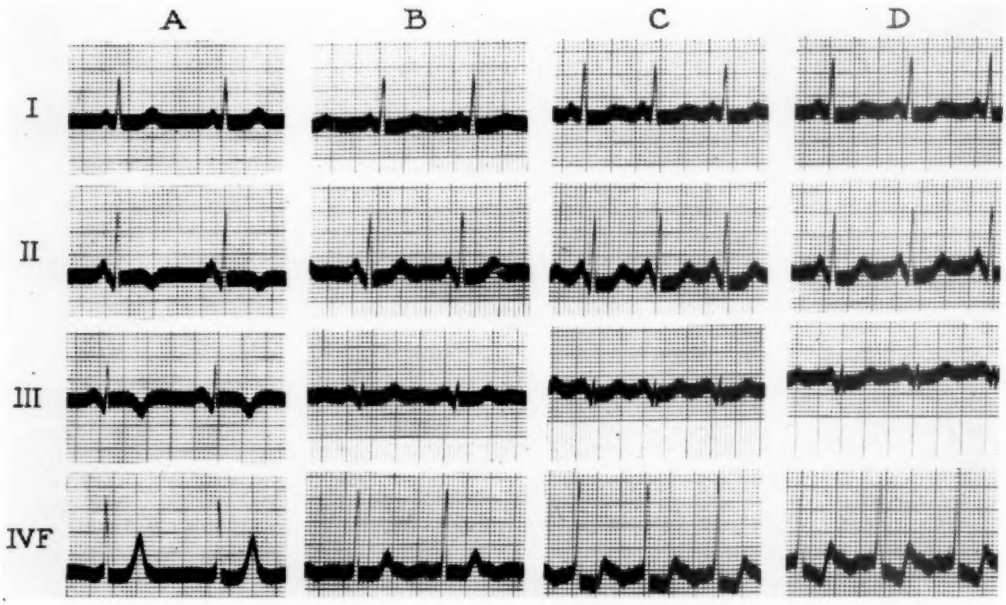

Fig. 7.—G. M. Man, 50 years of age, with coronary heart disease and anginal pain. Moderate smoker. *A*, Two weeks after cardiac infarction. Nicotine study made three months later. *B*, Control. Needle in vein. Rate, 90; blood pressure, 140/80. *C*, Two minutes after injection of 2 mg. nicotine bitartrate. Rate, 120; blood pressure, 144/86. *D*, Fifteen minutes after injection. Rate, 102; blood pressure 148/82. No anginal pain; complained of dizziness and tingling.

Determinations of cardiac output after smoking were made in five normal persons by Grollman,[13] using the acetylene method. His results, like ours, were variable, with increases ranging from 0.1 to 1.3 liters per minute. The largest increase was observed in an habitual cigarette smoker after he had smoked three cigars. Another cigarette smoker, after smoking two cigars, showed an increase in output of only 0.1 liter per minute. Moderate smoking yielded intermediate values.

In 1912, Cannon, Aub, and Binger[14] demonstrated, in cats, that the intravenous injection of nicotine, in doses of 3.5 to 7.5 mg., resulted in augmented adrenal secretion. Such doses are comparatively much larger than those employed by us. It was of interest to know whether added liberation of epinephrine might play a part in causing the circulatory changes observed. In view of the technical difficulty in determining the amount of epinephrine in the blood, a rise in the level of the blood sugar appeared to offer an indirect though crude

indicator of adrenal stimulation, for it has long been known that an increase of epinephrine in the blood induces hyperglycemia.

Widely different effects on the level of the blood sugar after smoking have been described by various investigators and these have been summarized by Dill and associates.[15] Increases of 10 to 40 per cent after one cigarette, and a decrease of 27 per cent after one cigar, have been reported. Other authors have noted both increases and decreases.

Dill's group made frequent determinations after the inhalation of the smoke of one cigarette in the course of five to ten minutes. The amount of nicotine absorbed was thus comparable to the dose injected in our studies. Nine-tenths of the observations, in their ten fasting subjects, were within 5 per cent of the rest level. The fluctuations in our subjects were wider, but, in both series there was no consistent trend, either upward or downward.

It is possible that the amount of epinephrine effective in causing changes in the cardiovascular system is smaller than that necessary to raise the blood sugar. Because of the relatively small dose of nicotine injected and the failure to induce hyperglycemia, it seems improbable that an increase in adrenal secretion was responsible for the circulatory reactions observed. In any case, these were initiated by nicotine.

SUMMARY AND CONCLUSIONS

1. Intravenous injections of 2 mg. of nicotine bitartrate were given to forty-six subjects. These included eighteen normal persons, twenty-four patients with coronary heart disease, and four with peripheral vascular disease. Observations were made on changes in the heart rate, blood pressure, cardiac output, and electrocardiogram. The symptoms produced were noted.

2. The amount of nicotine alkaloid contained in 2 mg. of the bitartrate is approximately 0.6 milligrams. This corresponds to the estimated amount of nicotine absorbed on inhaling the smoke of a cigarette five times in the course of one minute.

3. A comparison was made of the average changes observed in heart rate, blood pressure, and cardiac output in the normal group, in the patients with coronary heart disease, and in those with peripheral vascular disease. No significant differences between the three groups were apparent on statistical analysis. There was much less variation in repeated tests in the same individual than in different individuals.

4. There were no significant differences in reaction between smokers and nonsmokers in any group.

5. After the injection of nicotine, slight changes in the electrocardiogram were observed in some members of all groups. Significant changes were observed in four patients with coronary heart disease. In two of these, who suffered from spontaneous anginal attacks, pain was associated with the appearance of electrocardiographic changes.

6. In all groups, individual differences in sensitivity to nicotine were evident in the number and severity of the symptoms which followed its injection.

The most frequent complaint was dizziness. Other symptoms were tingling, faintness, and nausea. Vomiting and brief circulatory collapse occurred in one normal young man who had never smoked.

7. Nicotine injection caused no consistent variations in the level of the blood sugar in fasting subjects, although there were fluctuations both upward and downward. Because of the small dose of nicotine injected and the failure to induce hyperglycemia, it seems improbable that augmented adrenal secretion was responsible for the circulatory reactions observed. In any case, these were initiated by nicotine.

8. Variation in the effects of nicotine on the circulation is as great in patients with cardiovascular disorders as in normal persons. This variation depends to a greater extent upon individual susceptibility than upon the presence of disease.

9. In some patients with coronary heart disease, the injection of nicotine induces a state of coronary insufficiency. This may be the result of constricting the coronary arteries or of increasing the work of the heart. Probably both mechanisms are concerned.

We are indebted to Dr. John W. Fertig, Professor of Biostatistics, College of Physicians and Surgeons, Columbia University, for his help in making the statistical analyses.

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FRACTIONAL CIRCULATION TIMES USING FLUORESCENT TRACER SUBSTANCES

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LOCALIZATION of altered cardiovascular dynamics has been difficult[1] using the commonly employed techniques,[2-5] and the clinical applications of circulation time measurements have been limited by the inability to determine minimal circulatory retardation. These obstacles can be minimized by utilizing the newer tracer methods,[6,7] by means of which measurements to various regions of the body and measurements over longer segments of the cardiovascular system can be made. The purpose of this paper is to (1) demonstrate the use of riboflavin as a fluorescent tracer substance, (2) present a technique which renders circulation time measurements of greater clinical value, and (3) demonstrate the value of fractional circulation time measurements.

GENERAL METHOD

The technique employed was to raise a histamine wheal[8] (0.1 c.c. of a mixture of equal parts of 1:1,000 histamine phosphate and 2 per cent procaine) on various portions of the body to which the circulation time was to be measured. The volar surface of the forearm near the antecubital fold was used for arm-to-arm times and the dorsum of the foot was used for arm-to-foot times. After approximately one minute, or during the developing phase of the wheal, a fluorescent material was injected into an antecubital vein. The time was measured from the beginning of the injection to the first appearance of yellow-green fluorescence in the periphery of the wheal. Flourescence was excited by a 100 watt CH-4 spot ultraviolet lamp, fitted with a Corning 586 filter with maximal emission at 3,600 A° units.

Three groups of subjects were studied: (1) normal individuals, (2) those with heart disease with minimal evidence of cardiac failure, and (3) patients with marked left and right ventricular congestive heart failure. Patients with peripheral vascular disease were excluded. The room temperature was approximately 83° F. unless otherwise stipulated.

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A COMPARATIVE STUDY OF FLUORESCENT AGENTS USEFUL IN THE OBJECTIVE DETERMINATION OF CIRCULATION TIMES

A number of fluorescent materials were studied in vivo and in vitro. Atabrine, theophylline, certain xanthine derivatives, acriflavine, riboflavin, and fluorescein all showed some degree of fluorescence. Of these, riboflavin* and fluorescein were satisfactory for clinical use, being relatively diffusible in tissue spaces and easily visible, and giving sharp end points in a darkened room. The entire dosage of riboflavin or fluorescein could be administered in 2 c.c. of fluid. Riboflavin, however, was not painful when injected subcutaneously, and was technically easy to administer because of its transparency.

The concentration and dosage of riboflavin and fluorescein necessary for maximum fluorescence in vitro was determined by means of the fluorophotometer. Peak fluorescence of riboflavin was produced at a concentration of 8 x 10^{-5} moles per liter (Fig. 1). Peak fluorescence for fluorescein occurred at con-

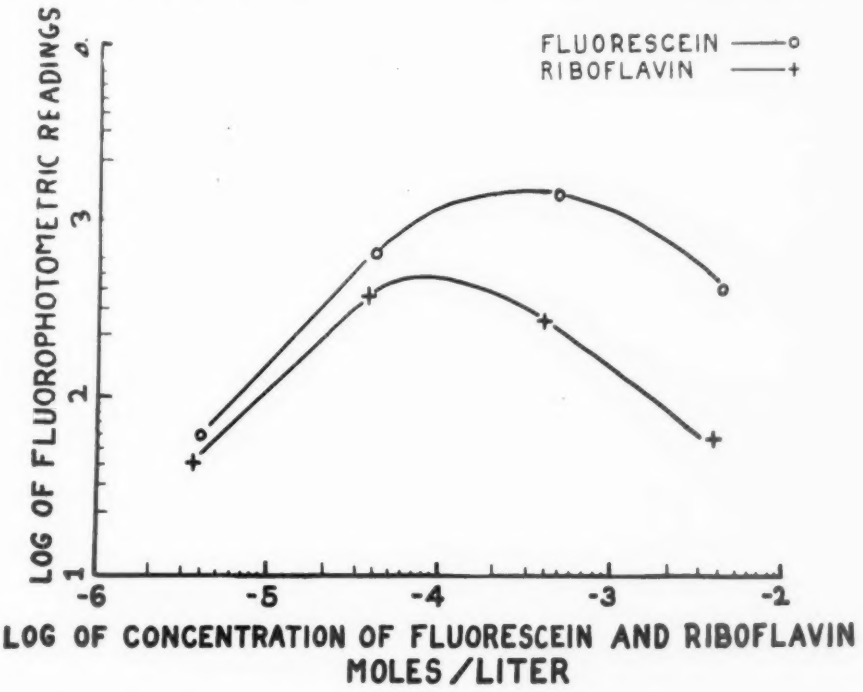

Fig. 1.—Relation between concentration of riboflavin and fluorescein and degree of fluorescence.

centrations approximately ten times as great. It was calculated from the approximate dilution in the body that the amount of riboflavin for optimum fluorescence was 0.5 mg. per kilogram and for fluorescein 5.0 mg. per kilogram of body weight. In vivo studies revealed that 0.8 mg. per kilogram of body weight of riboflavin

*Flavaxin "Niphanoid" supplied by Research Laboratory, Winthrop Chemical Co., Inc., New York, N. Y.

and 5.4 mg. per kilogram of body weight of fluorescein were desirable for satisfactory results due, perhaps, to the interference of the overlying integument and/or to the quenching effect of electrolytes of fluorescence.

Arm-to-arm riboflavin and fluorescein circulation times were compared in ten normal adults and in fifteen cardiac patients with varying degrees of congestive failure. Determinations were made at twenty-four-hour intervals (Fig. 2). The average fluorescein arm-to-arm time for the normal subjects was 18.6 seconds, the range being 13.5 to 25.6 seconds. The average riboflavin time for normal subjects was 19.1 seconds, the range being 14.5 to 26.2 seconds. In the cardiac patient the riboflavin time averaged 37.5 seconds and varied between 29.0 to 55.2 seconds. In these patients the fluorescein time averaged 33.5 seconds and varied between 19.0 and 45.2 seconds. A close correlation between riboflavin and fluorescein circulation times was present in both normal subjects and cardiac patients.

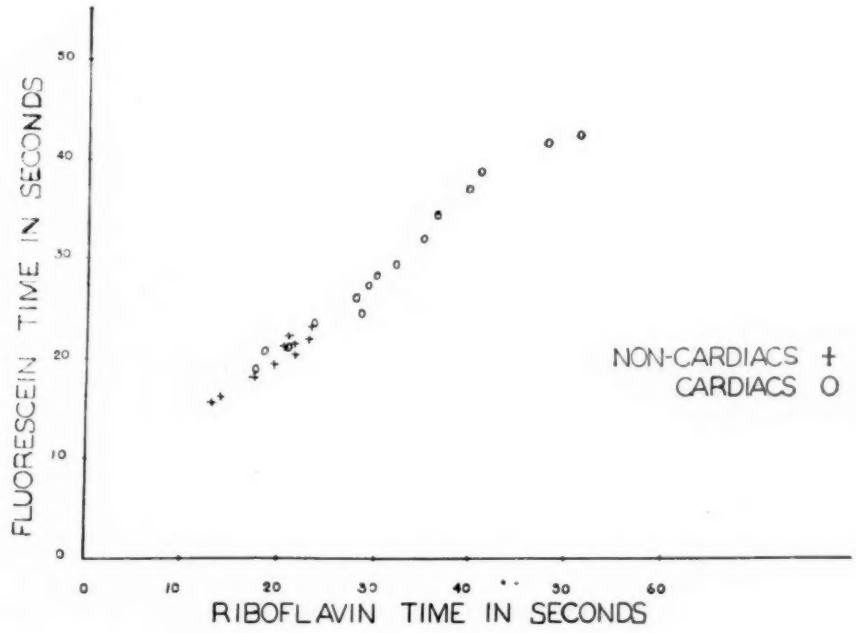

Fig. 2.—Relation between fluorescein and riboflavin times in twenty-five patients.

Arm-to-arm riboflavin times were determined in thirty-five normal individuals between the age of 14 days and 65 years (Table I). The shortest circulation times occurred in the youngest individuals. The shortest circulation time was 6.2 seconds and was encountered in the 14-day-old infant. The longest circulation time was 26.2 seconds. The average for the normal adult group was 19.1 seconds.

TABLE I. RIBOFLAVIN CIRCULATION TIMES (ARM-TO-ARM)

AGE	CARDIAC STATUS	NUMBER	CIRCULATION TIMES (SEC.)		
			MAXIMUM	MINIMUM	AVERAGE
14 Days-5.9 yr.	Normal	15	15.1	6.2	8.9
6-12.9 yr.	Normal	10	15.3	9.2	10.4
13-65 yr.	Normal	10	26.2	14.5	19.1

FRACTIONAL CIRCULATION MEASUREMENTS AND THE EFFECT OF ROOM TEMPERATURE

Circulation times through a short and long fraction of the cardiovascular system were determined. Arm-to-arm and arm-to-foot times were measured in ten normal individuals and in ten patients with marked clinical left and right ventricular congestive heart failure (Fig. 3). The average difference between

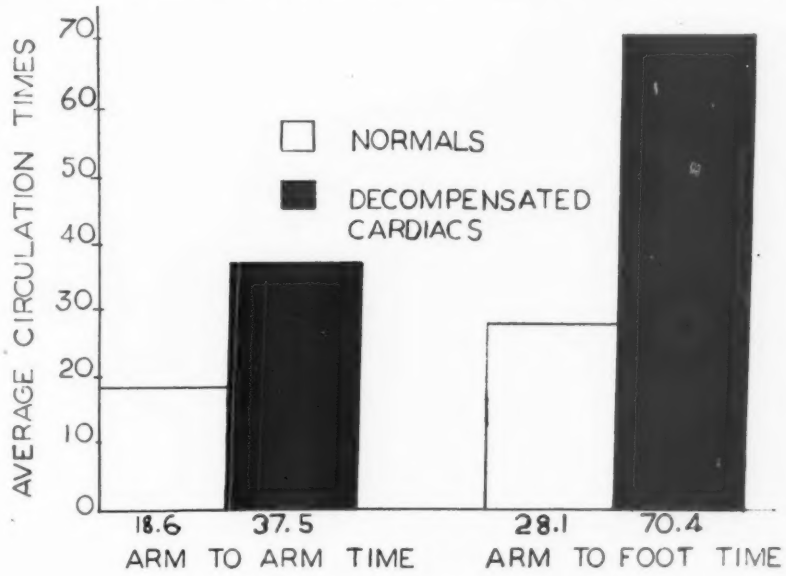

Fig. 3.—Circulation times in normal and decompensated individuals.

arm-to-arm times in normal individuals and in patients with congestive failure was 18.9 seconds, whereas the average difference between arm-to-foot times in the same groups was 42.3 seconds. These differences suggest that the arm-to-foot time is a more sensitive index of circulatory retardation than is the arm-to-arm time.

Circulation times through a systemic arterial segment were determined in normal individuals and in patients with minimal and marked congestive heart failure. The time through the arterial segment was computed by subtracting the arm-to-arm time from the arm-to-foot time (Table II). The average arterial circulation in normal subjects was 9.5 seconds and varied between 7.5 and 11.2 seconds. Among patients with minimal congestive heart failure in whom the arm-to-arm times were normal, the average arterial time was 14 seconds. A time greater than 12 seconds was suggestive of cardiac decompensation even though the arm-to-arm time was within normal limits. In severely decompensated patients, the average arterial circulation time was occasionally as long as 59 seconds.

TABLE II. CIRCULATION TIME DIFFERENCES (ARM-TO-FOOT TIME MINUS ARM-TO-ARM TIME)

	NORMAL (SEC.)	BORDERLINE (SEC.)	DECOMPENSATED CARDIAC (SEC.)
Average	9.5	14.0	32.9
Maximum	11.2	15.4	59.0
Minimum	7.5	13.8	14.9

The effect of room temperature on the appearance times of fluorescein and riboflavin was studied in ten normal and in ten decompensated cardiac patients. Patients were required to rest in a supine position for thirty minutes at a constant room temperature before determinations were made. Determinations were made at twenty-four-hour intervals first in a cold room (average 68° F.), then in a hot room (average 93° F.). Among normal individuals arm-to-arm times averaged 20 and 13 seconds in the cold and hot rooms, respectively. Among the decompensated patients the average times were 39 and 28 seconds, respectively. Arm-to-foot times in the normal group averaged 36 and 22 seconds in the cold and hot rooms, whereas the average for the decompensated patient was 79 and 50 seconds, respectively. Thus, it can be seen that room temperature has considerable effect upon arm-to-arm and arm-to-foot circulation times. Arm-to-foot times were affected to a greater degree than were arm-to-arm times. This was particularly true among the cardiac patients.

DISCUSSION

Riboflavin and fluorescein are useful in the objective determinations of fractional circulation times in man. Other objective methods, such as those employing sodium cyanide or histamine, are not suitable for fractional studies.

A suitable material for the measure of fractional times should fulfill the following requirements: It should be nontoxic and preferably not foreign to the body. The entire dose should be contained in a small amount of fluid, ideally not more than 2 cubic centimeters. It should be noninjurious and non-

painful if injected subcutaneously. It should fluoresce satisfactorily under a simple portable light source. It must be readily diffusible into tissue spaces. It should be clear and light in color. Of the substances studied, riboflavin and fluorescein most nearly fulfilled these requirements. Fluorescein* produced transient nausea in approximately 5 per cent of patients and vomiting in a smaller percentage. Burning on urination was occasionally encountered. Riboflavin was relatively free from side reactions; however, the degree of fluorescence was somewhat less than that of fluorescein. It is felt that riboflavin is the drug of choice for infants and children, since accidental subcutaneous injection is not painful and satisfactory fluorescence occurs using the wheal method. Fluorescein is probably the drug of choice for adults in whom there is no contraindication to its use.

Circulation time measurements over long segments of the cardiovascular system are often more sensitive in demonstrating the presence of left ventricular failure than are measurements made over shorter segments. A long segment of the arterial system is employed in determining the arm-to-foot circulation time. It was not uncommon for patients with congestive failure to exhibit normal arm-to-tongue times when calcium gluconate or sodium dehydrocholate were use and prolonged arm-to-foot times when riboflavin or fluorescein were employed. Such a finding occurred when minimal hypodynamic function of the left ventricle existed. Other factors such as peripheral vascular disease, polycythemia, and a cold environment might also be responsible for retardation of the circulation time. A cold environment produced prolongation of the circulation time particularly in the longer segments, that is, to the foot. It is felt that the effect of environmental temperature on the circulation is due largely to its action on the peripheral vascular system. Thus, if it is not possible to control the temperature of the room in which the test is performed, it may be preferable to record only measurements to the arm, a region which is probably affected by cold to a lesser degree.

Fractional circulation times in which the circulation time over isolated segments of the cardiovascular system are recorded are often of considerable importance in patients with altered cardiovascular dynamics. By recording the arm-to-arm and arm-to-foot time and deriving the arterial segment time, information not obtained by a single reading is found. For example, it has recently been shown that the circulation time increases with enlargement of the heart and that a prolonged time may be indicative of cardiomegaly and not of congestive failure. Determination of the arterial segment time cancels out the cardiac factor inherent in arm-to-arm and arm-to-foot times and thus gives information which is not altered by cardiac size.

The diagnostic value of fractional circulation times may be illustrated by the following: (1) The normal adult with readings recorded in a warm environment should have arm-to-arm times ranging from 15 to 25 seconds, arm-to-foot times of 25 to 35 seconds, and arterial segment times of 7 to 12 seconds. (2) With isolated right ventricular failure, the fractional times would be prolonged to the

*E. F. Kirk Co., New York, N. Y.

arm and foot, while the arterial segment time would be normal. (3) Patients with left ventricular forward failure may have normal or borderline arm-to-arm times and long arm-to-foot and arterial segment times. (4) Patients with right and left ventricular failure characteristically exhibit prolongation of all three times. (5) Patients with hyperthyroidism have all times accelerated.

The principles involved in the localization of segmental dynamics may be applied to other segments of the cardiovascular system.

SUMMARY

Riboflavin is a useful fluorescent tracer substance which is of particular value in determining the circulation times in infants and children.

Properly controlled circulation times to the foot are, under certain circumstances, a more sensitive measure of congestive heart failure than are measurements made to shorter segments of the cardiovascular system.

Fractional circulation times are useful in comparing circulatory dynamics in various regions of the body and are an aid in the diagnosis of certain cardiovascular states.

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THE SYNDROME OF RUPTURE OF AORTIC ROOT OR SINUS OF VALSALVA ANEURYSM INTO THE RIGHT ATRIUM

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MODERN clinical medicine has advanced slowly but definitely by careful descriptions of symptoms and signs correlated with post-mortem findings. In a series of cases with similar anatomical lesions and very definite and clearly described ante-mortem clinical pictures, the symptoms and signs of differential diagnostic value may be grouped together in syndromes. Careful analysis of symptoms and signs of each dramatic episode which is produced by rupture of the aortic root into an adjacent great vessel or into one or another heart chamber may add to the definite clinical criteria of the condition.

As early as 1842, Hope[1] associated the clinical picture and physical phenomena of the rupture of the dilated aorta into the pulmonary artery. He cited three cases: one reported by Payne and Zeink in 1819, one reported by Willis in 1825, and one studied by himself in 1833. Scott[2] in 1924 and Porter[3] in 1942 reviewed other cases that have been reported, and from these isolated reports and experiences with three complete cases, the syndrome of rupture of an aortic aneurysm into the pulmonary artery was delineated.

Pepper and Griffith[4] in 1890 described the clinical symptoms and diagnostic physical signs that follow the establishment of a communication through an aortic aneurysm between the aorta and the superior vena cava. Later in 1940, this syndrome was restated by Armstrong, Coggin, and Hendrickson.[5]

The syndrome that is produced by the rupture of an aneurysm of the aorta into the conus arteriosus of the right ventricle was described by Laycock[6] in 1860, by Lichtenberg[7] in 1865, by Schwab and Sanders[8] in 1931, by Tompkins[9] in 1941, and by Harris and Shattenberg[10] in 1944.

Isolated cases of rupture of an aortic sinus aneurysm into the right atrium were described by Charcot[11] in 1860, by Higgins[12] in 1934, and by Wright[13] in 1937. Single cases of congenital false aneurysm and rupture through defects of the aortic septum have been recorded by T. H. Gage[14] in 1863, by Abbott[15] in 1919, by Micks[16] in 1940, and by Shepherd, Park, and Kitchell[17] in 1944. Ruptured aneurysm of the sinus of Valsalva was found four times in 3,000 autopsies by Ostrum and his associates.[18] The condition was present in slightly less than one per cent of a series of 5,896 autopsies reported by Snyder and Hunter.[19] While a

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congenital aortic septal defect presumably was the basic cause for the development of a fistula between the aorta and the right heart in some cases, the causative disease in most cases, and even in most of the cases that have taken origin from the aortic sinuses, was syphilitic aortitis and aortic aneurysm.

Aneurysms of the aorta have been found in about 0.25 per cent of all patients autopsied, and of those dead with aortic aneurysm, more than 50 per cent died of rupture, according to Kampmeier[20] and Brindley and Schwab.[21] The usual sites of the rupture were into the left pleural cavity, pericardium, esophagus, right pleural cavity, vena cava, and left main bronchus. Aneurysms of the extreme aortic root and of the sinuses of Valsalva were more often syphilitic than congenital in etiology in our local series. These were more prone to result in acquired intracardiac arteriovenous communications or fistulas than were supravalvular aneurysms.

We feel that the development of a fistula from the aortic root into the right atrium, although less common, is spectacular enough, just as is rupture into the pulmonary artery or into the superior vena cava, to produce a distinctive syndrome. Besides the cavity or vessel into which the penetration occurs, the size of the fistula determines, to a large extent, the clinical picture and the length of time of survival after the accident. The added strain on the heart is usually more than the myocardium can compensate for and the sudden failure is often overwhelming and fatal. One of our patients lived for seven days while the other was under observation for about three years after the fistula developed.

The clinical and post-mortem findings in two carefully studied cases of abnormal communications between the aortic root and the right atrium will be presented. Comparison of these findings with data from the literature and from our cases of penetration from the aorta into the right ventricle, the conus arteriosus, the pulmonary artery, and into the superior vena cava constitutes the data upon which our description of the syndrome is based.

CASE 1. (*Syphilitic Aortic Aneurysm That Ruptured Into the Right Atrium*).—E. B., (No. 54757, P. M. 4339), a 35-year-old Negro butler, was admitted to the hospital on April 13, 1937. While serving at a dinner party on April 6, 1937, he had suddenly felt, in rapid succession, a shortness of breath, extreme weakness, particularly marked in the arms, and an excruciating pain in the chest. The pain began in the midsternal line on a level with the nipple and extended downward as far as the umbilicus. It was cramp-like and associated with a sense of constriction, epigastric fullness, and abdominal tension. The patient noticed that his heart began to "jump and beat fast". He had not lifted anything heavy or made any undue physical effort. He returned to his home where he remained for six days, too ill to go to the hospital. His symptoms increased in severity. Weakness was extreme and he could scarcely get his breath. He could not lie down and whenever he would drop off to sleep, he would wake up gasping. A cough began and was productive of light, clear, and thin mucoid sputum which later became dark and thick with blood. Vomiting occurred and continued for a few days accompanied by loss of appetite. Pain in the abdomen became generalized but was most severe in the umbilical region. A bloody stool was passed before hospitalization. He developed swelling of the ankles together with a general increase in edema. He noted no fever.

The patient had worked as butler and chauffeur since 1928 and previously had done heavy work as a stevedore. He had been married twice. There had been no pregnancies in either marriage. In 1923 he acquired gonorrhea and syphilis. He was given only local treatment. His blood was examined by one physician and reported negative. He had smallpox at the age of 8 years. He had no symptoms preceding the onset of his attack.

Physical Examination.—Physical examination showed a very muscular, moderately obese Negro measuring 71 inches in height, and weighing 212 pounds. He was in acute respiratory distress and was orthopneic. His face appeared swollen. The neck veins were distended and pulsated. The whole chest seemed to pulsate. The apex impulse was in the fifth intercostal space. A prolonged, intense systolic thrill was felt most intensely over the midsternum at the level of the fourth rib but could be felt in the epigastrium. Pulsation of the engorged liver was palpable. A machine type of murmur was audible over the precordium, with systolic accentuation and maximum intensity at the third and fourth costal cartilages, and transmitted to the right and downward into the epigastrium and right upper abdomen. The systolic murmur was heard widely. The diastolic murmur was somewhat different in character. It was loud, was best heard in the subaortic area, and was transmitted down the sternum to the right, with maximum intensity at the level of the fourth rib. It could also be heard in the epigastrium (Fig. 1).

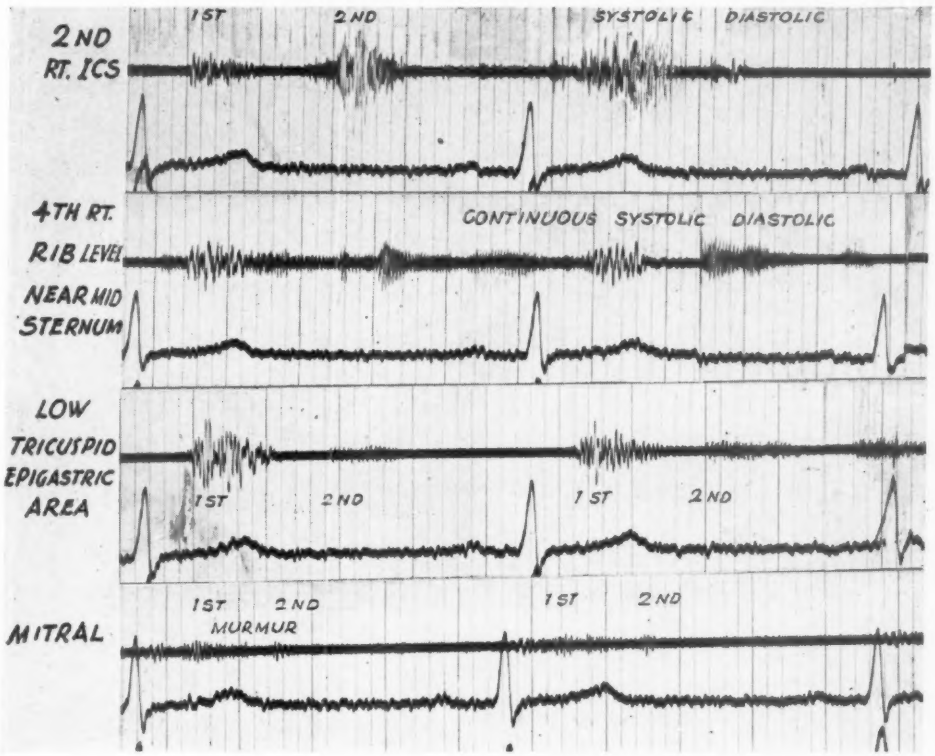


Fig. 1.—Phonocardiograms made in Case 1.

The lungs were hyperresonant and no râles were heard. The abdomen was full and rounded. Pulsations could be seen and felt in the epigastrium. The liver was engorged, and extended 5 to 6 cm. below the costal margin. Its edge was tender, smooth, and rounded. The genitalia showed an old scar on the corona. The extremities were cold and clammy. The muscles were weak, even though large and bulky. The dorsalis pedis pulses were palpable. The pressures in the brachial arteries were 120/54 on the right and 110/58 on the left; in the femorals, 144/68 on the right and 154/78 on the left. Loud pistol shot sounds were heard in both femoral arteries. The general venous pressure was considerably elevated.

An electrocardiogram made on April 13, 1937 showed right axis deviation and paroxysms of atrial tachycardia with A-V block (Fig. 2). Stethocardiograms taken April 10, 1937 showed a continuous systolic and diastolic murmur (Fig. 1). A two-meter teleroentgenogram showed a conspicuous increase in the cardiac measurements. The measurements were: transverse chest diameter, 30.5 cm.; transverse cardiac diameter, 20 cm.; length, 20 cm.; midline to left border, 12 cm.; midline to right border, 8 cm.; and aortic arch, 7 centimeters.

The blood hemoglobin was 80 per cent or 10.8 Gm. per cent, erythrocytes 4,500,000, and white blood cells 15,000; with 72 per cent neutrophiles; 23 per cent lymphocytes, 2 per cent monocytes, 2 per cent eosinophiles; and 1 per cent basophiles. Filament count was 88 per cent and nonfilament count, 12 per cent. Serologic tests revealed a Kolmer reaction of 2 plus and a positive Eagle test.

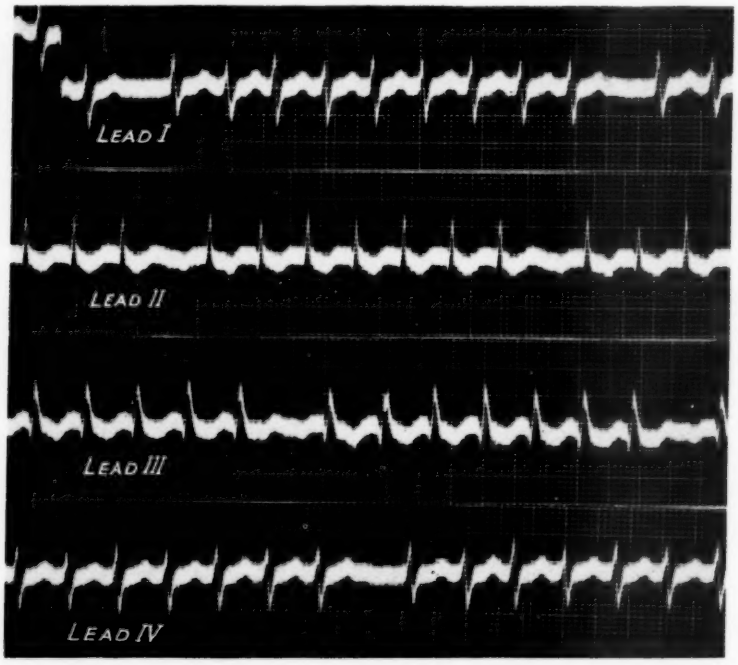
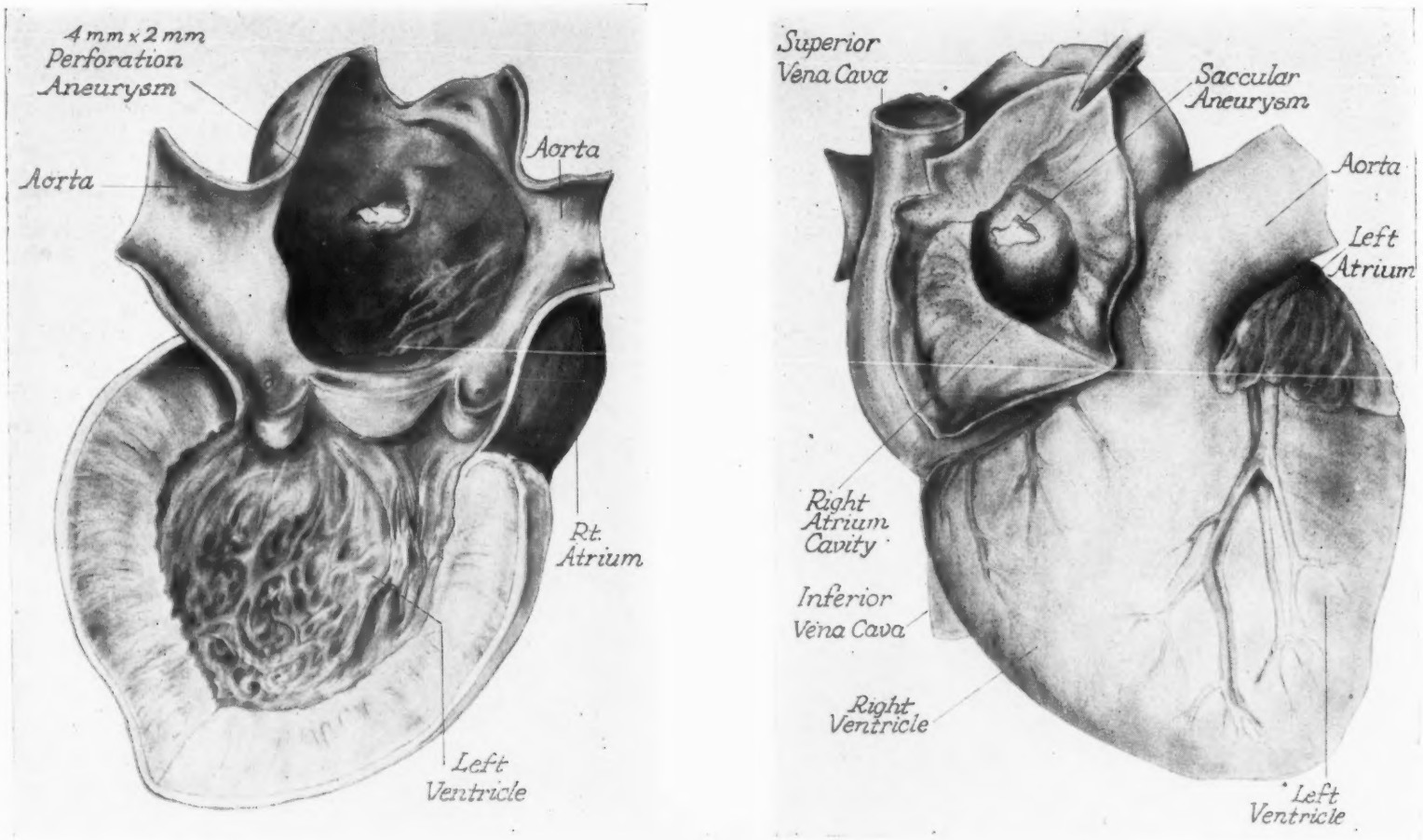


Fig. 2.—Electrocardiogram made in Case 1, showing terminal paroxysmal tachycardia with occasional A-V block.

Clinical Course.—The clinical course was stormy with the patient suffering constantly from orthopnea which was unrelieved by morphine. Congestive failure was extreme with engorgement of the lungs and liver. There was hemoptysis and pulmonary edema, the patient gasping for breath. He died on April 13, 1937, seven days after the acute onset of distress. A diagnosis of an aortic root aneurysm with rupture into the right atrium was made.

Post-mortem Examination.—The body was that of an obsese Negro man. There was approximately 300 c.c. of bloody fluid in the right pleural cavity and practically no fluid in the left pleural cavity. The pericardial cavity contained approximately 100 c.c. of bloodstained fluid. There were delicate adhesions between the distended right atrium and the parietal pericardium on the right.

The heart weighed 505 grams. The right atrium, the right ventricle, and the large veins leading into the right atrium were markedly distended with blood. Opening of the right atrium revealed a torn opening in the right wall medially (Fig. 3, *A* and *B*). On probing this opening



A. B.

Fig. 3.—*A*, Drawing of the heart in Case 1, showing the left ventricle opened and the aorta split between the two anterior cusps, and the aortic aneurysmal bulge with the site of the ragged 4 mm. by 7 mm. rupture.

B, Drawing of the heart in Case 1, showing the right atrium opened with the irregular fistula from the aneurysmal sac into the right atrium.

it was found to lead directly into a moderate sized aneurysm of the aorta. The diameter of this tear was approximately 2 by 8 millimeters. The opening into the aorta also had the irregular edges of a recent rupture. The tricuspid ring was dilated. The right ventricle was dilated. On the right lateral aspect of the very first portion of the aorta there was an aneurysm which bulged to the right and posteriorly against the right atrium. The orifice of this aneurysm was approximately 3 cm. in diameter. The greatest inside diameter of the aneurysm was approximately 9 centimeters. There was a small amount of clotted blood adherent to the lining of the aneurysm. The coronary arteries showed some atherosclerosis, but no narrowing except at the orifices.

The liver weighed 1,830 grams. It was slightly enlarged, firm, and had a distinct, diffuse, nutmeg appearance everywhere on the external surface which was visible through the capsule. On cut section, it showed a diffuse, mottled, reddish-brown and red nutmeg pattern typical of chronic passive congestion.

Pathologic Diagnoses: (1) Acute aortic-right atrial fistula due to recent rupture; (2) syphilitic aneurysm of first portion of aorta; (3) syphilitic aortic valvulitis and aortic regurgitation; cardiac hypertrophy (505 grams) and dilatation; (4) moderate aortic and coronary atherosclerosis, moderate general atherosclerosis; (5) fibrinous pericarditis, localized over the right atrium; (6) severe passive congestion of liver, spleen, and gastrointestinal tract; (7) cortical adenoma of left adrenal gland, undifferentiated; and (8) hemorrhage into the duodenum and mesentery.

The probable cause of death was acute heart failure following rupture of an aortic aneurysm into the right atrium of the heart. The autopsy confirmed the clinical diagnosis of aneurysm of the first portion of the aorta with rupture into the right atrium, syphilitic aortitis, aortic valvulitis with regurgitation, coronary atherosclerosis, and aortic arteriosclerosis.

CASE 2 (*Congenital Aortic Defect With Dissecting Aneurysm and Rupture Into the Right Atrium*).—I. J., a 44-year-old woman, was admitted to the hospital on Jan. 20, 1941. She had been hospitalized frequently for nine pregnancies from 1925 to 1936 when cystadenomata of the ovaries were removed. She stated that all of her life, even as a child, she had had peculiar distress and a fluttering sensation in the upper part of her heart. Her eighth pregnancy was complicated by pre-eclamptic toxemia. She had a blood pressure of 188/110, albuminuria, and anemia, but normal blood chemistry findings. She had gone into shock and had been given 50 c.c. of 50 per cent glucose. This was followed by a very violent reaction with a heart rate of 136 per minute and severe precordial pain. Her blood pressure had dropped to 78/50. In 1936, after recovery from the operation, her blood pressure had been 180/120 but it gradually became lower over a period of several years.

During succeeding years there were frequent hospital admissions. The patient always complained of pain which was sudden in onset, continuous and boring in character, and located between the second and fourth rib in the intercostal margin and the sternum. The pain radiated backward to the under surface of the scapula. In 1938 her blood pressure was 130/90. In 1939 and 1940 she had frequent attacks of precordial distress which radiated to the left shoulder and down the inner side of the left arm following exertion or emotional upset. There was accompanying shortness of breath and cough.

Frequent physical examinations had shown very few diagnostic signs. The aortic second sound had been found to be loud and tambour-like in quality and a soft blowing systolic murmur had been heard in the aortic area. Six serologic studies of the blood and one of the spinal fluid between 1925 and 1941 had shown negative Wassermann, Kolmer, and Eagle reactions.

The acute attack occurred on Jan. 17, 1941, at which time she had a very severe seizure of smothering and extreme weakness while straining at stool. There was a sense of excruciating tightness and pressure in her chest. She became quite dyspneic. Three days later, on Jan. 20, 1941, she was brought to the hospital. Her dyspnea had diminished but was still present. Epigastric distress had developed and the pain in the arm was still moderately severe. The right side of her face had become swollen and her voice was quite hoarse.

Physical Examination.—Physical Examination showed orthopnea and edema of the right eye, face, and neck. There was conspicuous congestion of the jugular veins, particularly notice-

able on the right with a strong positive venous pulse. Considerable heaving activity over the precordium and to the right of the sternum was present. A long continuous thrill with systolic accentuation was felt; its maximum intensity was at the level of the fourth costosternal junction and it was transmitted slightly to the right and downward along the right border of the sternum. The apex impulse was displaced to the left and indicated marked cardiac enlargement. A loud systolic and diastolic murmur with a rough machine-like systolic accentuation was present in the subaortic area. It was most intense at the level of the fourth rib and propagated along the right sternal border to the xiphoid and into the epigastrium as far as the umbilicus (Fig. 4).

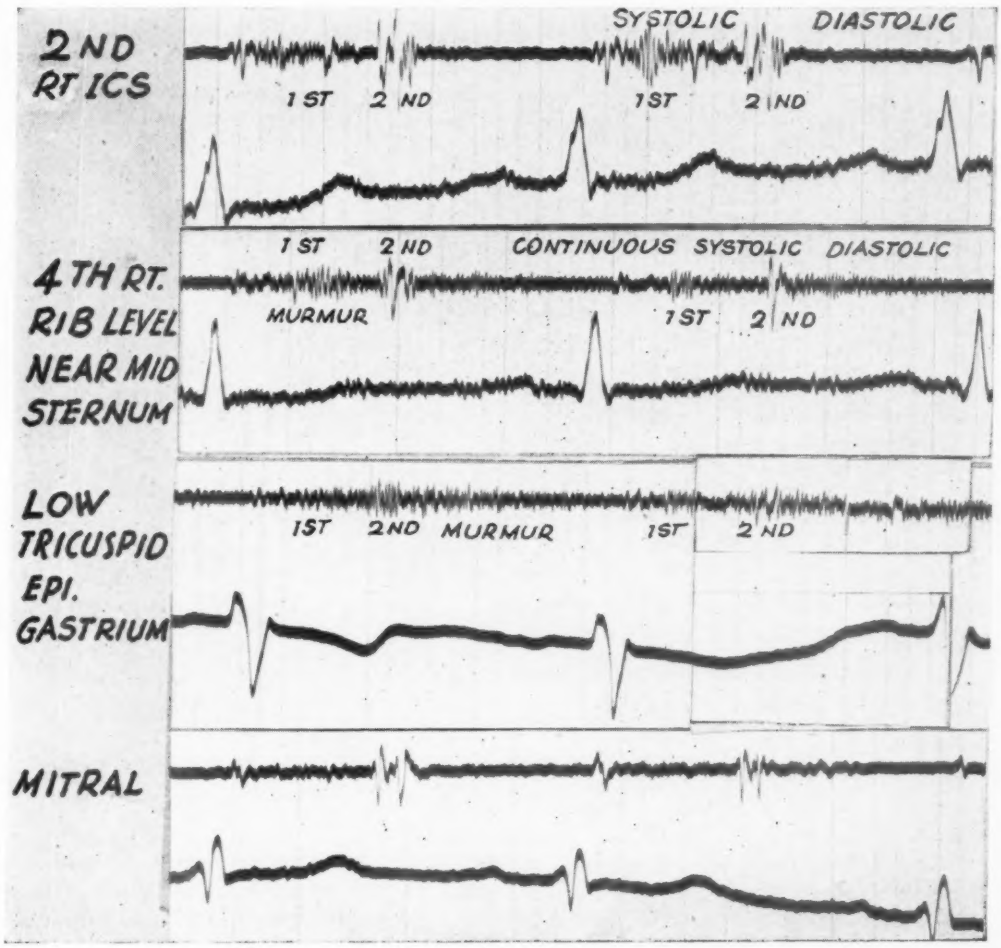


Fig. 4.—Phonocardiograms made in Case 2.

A water hammer effect was present in the carotid, brachial, and radial pulses. The blood pressure was 199/50 in both arms. Traube's pistol shot sound and Duroziez's diastolic murmur were heard in the compressed arteries. Capillary pulsations were visible in the finger tips. The venous pressure was 22.4 cm. of saline in the leg and 24 cm. in the arm. The abdomen was distended. The abdominal wall was thick and tense. The liver extended 4 cm. below the costal margin. It was smooth, slightly tender, and could be definitely felt to pulsate.

A roentgenogram showed massive increase in the cardiac shadow with an estimated increase of probably 50 per cent, with enlargement of both sides, in the right atrial as well as the left ventricular area. Kymoroentgenograms showed aortic timing quite late, suggesting the presence of aortitis.

Electrocardiogram showed left axis deviation, plus 34 degrees, and later right axis deviation and transient atrial fibrillation on Aug. 29, 1941 (Fig. 5).

The blood count showed hemoglobin, 73 per cent; erythrocytes, 3,500,000; white blood cells, 6,000; the differential count was normal. Five Kolmer and Eagle tests were negative. Blood cultures were negative. The circulation time with alphalobeline was 15 seconds, and with ether, 10 seconds.

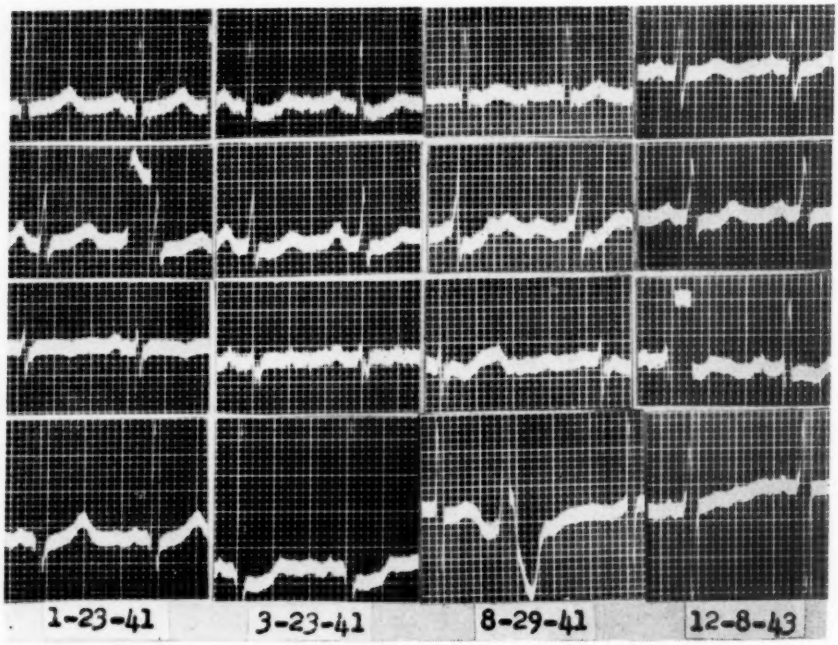


Fig. 5.—Electrocardiograms made in Case 2, showing a change in the electrical axis from left to right and atrial fibrillation on Aug. 29, 1941.

After two months in the hospital the patient was allowed to go home. Between March, 1941, and Jan. 17, 1944, she attended the outpatient clinic and was frequently admitted to the hospital for periods of one to two months because of congestive heart failure. She required mercurial diuretics and paracentesis. She had frequent attacks of precordial pain which were relieved by nitroglycerin. Occasional sharp thoracic pain was followed by hemoptysis. She occasionally had severe abdominal pain which was relieved by magnesium sulfate. Atrial fibrillation was recorded at times in the electrocardiograms. She was quite irrational at times when in congestive failure, and during her last admission she had to be restrained. She occasionally developed acute pulmonary edema which finally caused her death three years after the sudden development of her dramatic clinical picture.

Post-Mortem Examination.—Autopsy showed a large, but emaciated, middle-aged Negro woman. The nails were cyanotic. There was pitting edema of the feet and ankles.

The right pleural cavity contained an estimated 1,500 c.c. of straw-colored fluid and the left, 700 cubic centimeters. The pericardial sac showed scattered string-like adhesions over the right atrium anteriorly.

The heart weighed 480 grams. The epicardium, except for the adhesions, was smooth and glistening. The coronary arteries showed moderate atherosclerotic changes. The right atrium presented an aneurysm of its anterior wall, 4 cm. in diameter, which communicated with the aorta through a smooth fistulous opening 6 mm. in diameter (Fig. 6, *A* and *B*). The myocardium of the right ventricle was 6 mm. in thickness, while that of the left was 17 millimeters. The myocardium was pale and soft and showed no gross signs of infarction. The valves showed no gross pathologic processes.

There was an old lower midline abdominal scar 16 cm. long. There was a recent right lower quadrant puncture from which a pale, clear fluid was oozing. The peritoneal cavity contained an estimated 2,000 c.c. of clear yellow fluid. The liver was brown, small, and finely cirrhotic. Cut section revealed a very firm parenchyma. The gall bladder was small, 5 cm. by 1 cm., and contained an estimated 5 c.c. of light brown bile. The ducts showed no dilatation or angiitis.

The pathologic diagnoses were: (1) Chronic aortic-right atrial fistula probably beginning in a congenital defect of the wall of the aorta; cardiac hypertrophy (480 grams) and dilatation; congestion of the viscera. (2) Hydrothorax, ascites, and dependent edema. (3) Edema of the mucosa and extravasation of blood into the alimentary canal. (4) Cirrhosis of the liver and nephrosclerosis. (5) Cerebral edema.

The cause of death was congestive heart failure. The clinical diagnosis of an aortic-right atrial fistula was substantiated by the post-mortem studies. The congenital etiology had been only lightly considered because of the long history of substernal discomfort, the good obstetrical history, and the repeatedly normal serology. The dissecting aneurysm of the right atrium was an unexpected finding. The conditions found are shown in Figs. 6, *A* and *B*.

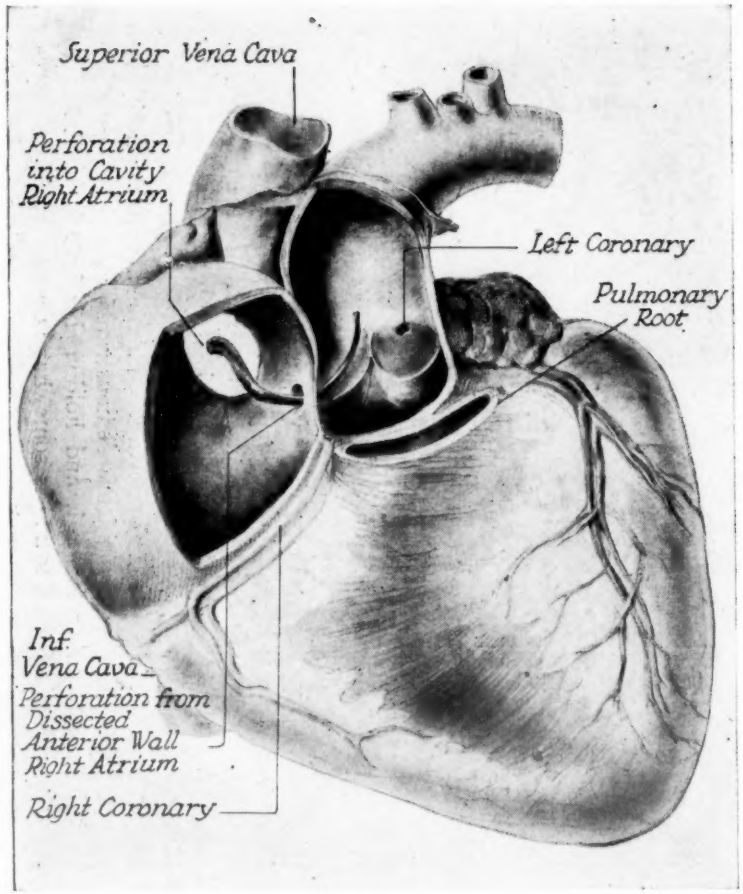
DISCUSSION

Ruptures of an aortic root aneurysm or aortic sinus aneurysm into the right atrium, right ventricle, conus arteriosus, pulmonary artery, or superior vena cava all present many similar dramatic symptoms and signs. The symptoms and signs, however, vary somewhat according to the size and site of the fistula. Distinctive characteristics develop according to the chamber or the vessel into which the communication has been made.

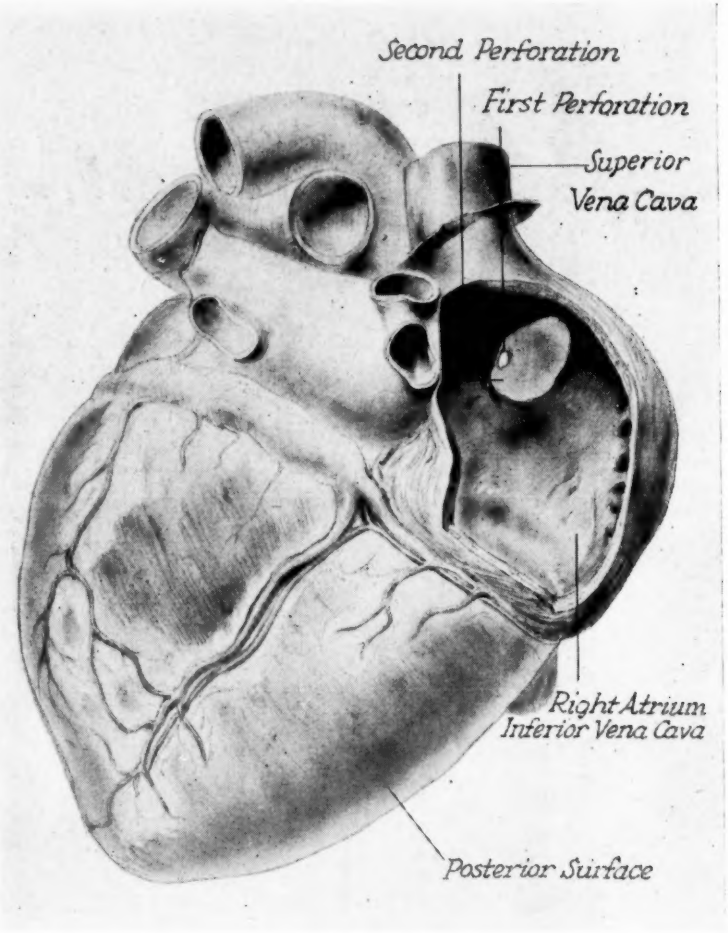
General symptoms such as premonitory boring, aching, aortic root pain, or substernal burning sensation are commonly produced by all progressing aortic root aneurysms, whether congenital, syphilitic, arteriosclerotic, or mycotic in etiology.

In the acute stage, extreme dyspnea may obscure other symptoms, but collapse, shock, exhaustion, and weakness may inaugurate the attack. Dyspnea is more severe when the fistulous tract from the aortic root leads directly into the pulmonary artery, conus arteriosus, right ventricle, or right atrium, than when the pentration is into the superior vena cava. Aortic root aneurysmal pressure may partially or even completely obstruct the pulmonary artery and produce temporary or constant pulmonary stenosis before penetration takes place and thus give premonitory symptoms and signs.

When the A-V fistula is between the aorta and pulmonary artery, the thrill and murmur are primarily systolic and are demonstrated most intensely with the patient sitting up, leaning forward, and holding his breath after forced exhalation. The pulmonic second sound is somewhat accentuated in all intra-



A.



B.

Fig. 6.—*A*, Drawing of the heart in Case 2, showing the anterior wall of the aorta and the right atrium cut away to demonstrate the defect in the right aortic wall. This extends from just above the right anterior aortic cusp, as shown by the curved needle, into the separated layers of the anterior wall of the right atrium. The dissecting aneurysm of the atrium communicated with the right atrial cavity posteriorly through the large oval clear window at the eye-end of the curved surgical needle.

B, Drawing of the heart in Case 2, showing the posterior aspect with the wall cut away to demonstrate the cavity of the right atrium with the large oval window from the dissecting atrial intramural aneurysm.

cardiac A-V communications, but is palpable and most strikingly augmented in the presence of direct penetration of the pulmonary artery. Dilatation of the pulmonary ring adds a high-pitched diastolic element. Dilatation and excessive pulsation of the pulmonary artery may be demonstrated and aneurysms may or may not be visualized.

The pulmonary conus arteriosus becomes much more prominent when the communication is directly into the conus, and secondarily so in penetration into the pulmonary artery from an aortic root aneurysm; especially when there has developed sufficient back pressure to produce pulmonary regurgitation as a result of dilatation. Physical and radiologic examination may reveal bulging and expansile pulsation of the part into which the aortic blood regurgitates.

Aortic root aneurysmal pressure may partially or even completely obstruct the pulmonary artery and produce temporary or constant pulmonary stenosis before penetration takes place; thus premonitory symptoms and signs should be demonstrable if looked for.

An aneurysm eroding into the right ventricle may involve the interatrial septum, the atrioventricular conduction pathway, or the intraventricular septum and the major branches of the A-V bundle. Anterior bulging and erosion from the root of the aorta may involve the coronary orifices or arteries and produce an anginal syndrome. The clinical picture of an extreme interventricular septal defect may be produced by pressure necrosis of the septum.

Acutely acquired communication between the aortic root and the right heart, in most cases, averages about three days of survival after rupture; in an exceptional case, the lesion has apparently been borne for possibly two months.

Right-sided heart failure, with elevation of the venous pressure, engorgement of the liver, and edema, develops promptly regardless of what part of the right heart or contiguous great venous system receives the blood. Cyanosis and edema of the face are not necessary or significant phenomena. Engorgement of the neck veins with a positive systolic pulsation and pulsation of an engorged liver are more common in the presence of an aortic fistula into the superior vena cava or right atrium.

The peripheral arterial phenomena of aortic regurgitation of a free type, the high pulse pressure, the water hammer carotid, brachial, and radial pulses, Traube's pistol shot sound, Duroziez's diastolic murmur and visible capillary pulsations develop in degree according to the size of the aortic defect, but are common in all such lesions.

Venous pressure is higher, the neck veins are more engorged, and the systolic pulsations are more intense when the aortic blood is directed into the superior vena cava or into the right atrium. It is less intense with penetration into the right ventricle unless this simultaneously produces insufficiency of the tricuspid ring.

The purring systolic and diastolic thrill with maximum intensity in the systolic phase is present in all cases and localized according to the position of the lesion, but modified by the extent of the false aneurysms or the fistulous tract. Localization at the point of maximum intensity of the murmurs, 1 to 3 cm. to the left in the third intercostal space suggests penetration into the conus arteriosus

or into the main pulmonary artery. Extremely loud accentuation of the pulmonary second sound usually develops.

In aortic-right atrial fistulas, there is a long, harsh, rough, continuous murmur with its point of maximum intensity at the fourth left costal cartilage in the mid-sternum and propagated along the right sternum border and usually to the right of the sternum. This sign suggests penetration into the right atrium or right ventricle.

If the fistula ends in the right atrium, and an aortic-right atrial communication has been established, the diastolic phase of the murmur becomes longer and is transmitted much further down the right border of the sternum through the inferior vena cava to the epigastrium and into the liver which pulsates. This murmur is often heard best and seems very close to the ear when the patient is lying on the right side. The aortic second sound usually persists and may often be clearly heard, while the pulmonary second sound is unusually accentuated. Palpation reveals a continuous thrill and exaggerated pulsation very near the sternum in the third and fourth intercostal spaces.

The right atrium and inferior vena cava are usually more greatly dilated when the blood stream is directed into them and produce dullness and extension of their shadows to the right of the sternum. Atrial mechanism disorders such as paroxysmal tachycardia or fibrillation are precipitated. If the fistula is of significant grade, the right ventricle will promptly be called upon to carry an extra load. The cardiac outline is globular and not of the aortic type in spite of peripheral manifestations of aortic regurgitation. The right ventricle is subjected to considerably more pressure change and there is a tendency to further development of the right axis deviation when regurgitation is into the right heart.

The symptoms and signs of an arteriovenous fistula between the great vessels or into the chambers of the heart are quite similar. However, a differential diagnosis of the anatomic localization is usually possible. The anatomic relations and the direction and fate of the shunted blood mass must be taken into careful consideration and the abnormal circulatory dynamics visualized.

An acquired communication has an abrupt dramatic onset, while a congenital fistula presents symptoms only as complications develop.

The syndrome of aortic-right atrial fistulae is thus delineated: (1) Smothering, tightness, and fullness in the chest and right upper abdomen are significant symptoms. Cyanosis is not in evidence. Râles and pulmonary edema develop late. (2) The liver rapidly becomes engorged and acutely painful and pulsates. (3) The characteristic rough, to-and-fro thrill and the machine-like murmur with systolic accentuation has its area of maximum intensity very close to the midsternal region. The diastolic murmur is loudest when the patient is in the right lateral position. The long diastolic murmur is propagated best along the right border of the sternum. Both murmurs, but especially the diastolic, are transmitted conspicuously down the inferior vena cava to the liver and to the umbilicus. These peripheral phenomena in the inferior vena cava are characteristic. (4) The right border of cardiac dullness extends considerably to the right. The axis of the heart is transverse with the shadow bulging conspicuously to the right. The whole heart is enlarged, but the silhouette is more globular in con-

tour. (5) Paroxysms of atrial tachycardia and atrial fibrillation are common. The right axis deviation usually develops as the right ventricle overcomes the strain of the high pressure overfilling through the shunt. (6) The peripheral arteriolar phenomena are similar to those of aortic regurgitation, patent ductus arteriosus, or any of the acquired shunts from the aortic root to the other chambers of the heart, the pulmonary aorta, or the superior vena cava.

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NONGANGRENOUS FROSTBITE OF THE FEET

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TISSUE damage from cold is by no means rare in temperate and arctic latitudes, especially among those exposed by reason of occupation.[1] War enormously increases the number of people so exposed. Resulting casualties have been numerous and have contributed to the tactical situation in the famous Napoleonic expedition to Moscow, in World War I,[2] and in the recent conflict.[3-8]

Nomenclature of the clinical syndromes observed has included frostbite, trench foot, shelter foot, and immersion foot, to mention a few of the more common terms. The mechanism of production, pathologic physiology, morbid anatomy, and essentials of treatment have been summarized well by Wright and Allen.[10] Except for a variety of immersion foot seen in tropical waters,[5b] cold has been a common denominator in these variously named disorders; in our opinion their essential similarity, and not their relatively superficial differences, should be emphasized. For this purpose, the more inclusive term frostbite seems the best available term.*

The pathology of frostbite and burn have much in common, and a similar classification has been advocated by Webster, Woolhouse, and Johnston[7] and by Wright and Allen[10] as follows:

First degree—Minimum lesion involving the outer layers of skin and recoverable without tissue death (blistering or peeling).

Second degree—Damage to superficial layers of skin severe enough to produce desquamation only.

Third degree—Death to deeper skin layers and some subcutaneous tissues, sometimes involving loss of nails, tips of toes.

Fourth degree—Gangrene with loss of an extremity or notable portion thereof.

Judging from our experience in the European Theater of Operations, actual death of tissues can be a small part of the picture. Large numbers of soldiers with no more than second degree frostbite were completely disabled because of

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*In the European Theater of Operation, through command usage, trench foot came to be applied specifically to casualties incurred by infraction of foot discipline and, in that sense, analogous to self-inflicted wounds. Casualties so labeled were not eligible for the Purple Heart Award, although foot discipline was sometimes unsatisfactory through no fault of the individual soldier. Frostbite, on the other hand, was employed for injuries acquired despite prophylaxis which was considered adequate by forward echelons. This was an added source of confusion to nomenclature.

painful, tender, vasospastic* feet. Conversely, it was noted that when there was gangrene, circulation in adjacent viable portions was usually good.

It was not clear whether death of tissues and troublesome vasospasm bore a constant relationship to one another, or whether any of the intrinsic or extrinsic factors known to favor frostbite might contribute more to development of one or the other manifestation. It was, therefore, decided to study a sample 200 casualties of frostbite, data from whom is the subject of this report.

METHODS

The work was done in the 81st General Hospital, located in the Communication Zone, during the winter of 1944-1945. The hospital was well behind combat areas and casualties were received after passing through a battalion aid station, and generally one or more other installations, in the chain of medical evacuation. They arrived on litters by hospital train and were retained for definitive treatment; that is, until fit for duty or clearly disabled for longer than the period allowed by current evacuation policies of the Theater Surgeon. There was a policy of one hundred twenty days in force during the period of this study.

The intervals between arrival of the patients in a battalion aid station and admission to general hospital varied from one to forty-five days. A majority, 139 (69.5 per cent), were received in less than two weeks. Care en route was consistent in essentials. All patients had been evacuated by litter and kept off their feet. The feet had generally been exposed to air and no other cooling device attempted. Since there was no central heating, and it was winter, this was probably adequate in most instances. Tetanus antitoxin, sulfonamide, and penicillin had been given in many, but not in all cases. There were no instances of noteworthy infection in this group. Only one patient had sympathetic block by paravertebral injections prior to reception.

The patients chosen for study were taken consecutively as they arrived at the hospital, unselected beyond chance factors that guided them to this particular installation instead of to any one of many others operating similarly.

The group represented nearly all branches of combat troops, including vehicle drivers, cooks, and radio operators. There were no service units represented. Both ground and airborne troops were included, but most of the men were infantry riflemen.

A special history and physical examination form was devised to guide, coordinate, and standardize the observations and procedures of treatment in the various wards. The following data were made available by the cooperation, group discussions, and consultations among the several members of the medical staff concerned with the care of these patients.† One of us (D. V. H.) saw each patient personally several times, and at each stage of progress.

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*Vasospasm is used throughout this paper, for want of a more exact term, to indicate reduced circulation, apparent clinically as significant pallor, coldness, cyanosis, or rubor. It is the exact reverse situation from vasodilatation where local circulation is increased. Both terms actually describe net circulatory results rather than the divisions and status of peripheral vessels involved. It is commonly accepted, however, that the arterial radicals play a dominant role. The reader is referred to Discussion for further comments.

†We especially appreciate the cooperation of Major Louis Appel, Major Irwin Makovsky, Captain Isidore Rossman, and Captain Norman O'Farrell.

FINDINGS

The sample group of 200 casualties was considered first as a unit. Subsequently, in an effort to uncover the possible significance of special factors, several subdivisions were analyzed separately. The subjects of the study were all healthy as far as careful physical examinations, with special attention to the cardiovascular system and routine urinalyses, could determine.

General Survey.—

Age: One hundred five (52.5 per cent) of the entire group were 18 to 21 years of age; 35 (17.5 per cent), 22 to 25 years of age; 31 (15.5 per cent), 26 to 30; and only 29 (14.5 per cent), 30 years of age or older. Thus 85 per cent were under 30 years of age and most of these were under 21 years.

Length of Service: Most of the men, 131 (65.5 per cent), had served for a period of one to three years; 55 (27.5 per cent) had served less than one year; and 14 (7 per cent) had served three years or longer.

Combat Experience: The total time each individual had spent under combat conditions is shown in Fig. 1. Forty-six (23 per cent) had had less than a week's experience prior to onset of foot complaints, and eighty-four (42 per cent) had had less than three weeks' experience. The incidence of frostbite among veterans of more than three weeks did not vary significantly during the over-all period of forty weeks represented.

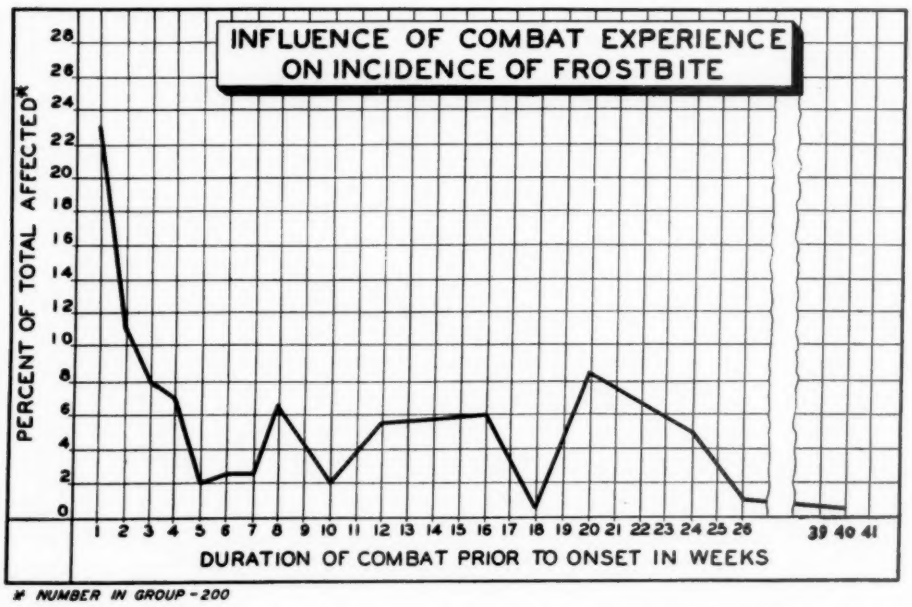

Fig. 1.—The incidence of frostbite in relation to combat experience of troops. Whereas the incidence does not vary materially among soldiers who had been in combat three weeks or longer (that is, forty weeks), it is substantially higher during the first month. In contrast, other forms of military experience and qualifications had no bearing. This seems to indicate the importance of practical field experience under combat conditions.

Rank: There were no officers among this group. One hundred seventy-four (87 per cent) were privates or privates first class, and twenty-six (13 per cent) were noncommissioned officers (corporals and sergeants), which is the standard U. S. Army distribution.

Parentage: One hundred one patients stated that their parents were American and were apparently of Northern European stock. There were 55 (27.5 per cent) whose origin was the British Isles; 10 (5 per cent), Italian; 20 (10 per cent), German; 5 (2.5 per cent), Scandinavian; 6 (3 per cent), Russian and Polish Jews; 1, Negro; and the remainder, mid-European.

Previous Frostbite: There were forty-four (22 per cent) who gave a history of known frostbite prior to the present illness.

Prefrostbite Symptoms: Pre-existing symptoms suggestive of circulatory disturbance of the lower extremities were given as shown in Table I.

TABLE I

Intermittent claudication*	14 (7.0%)
Paresthesia	17 (8.5%)
Blanching with cold	15 (7.5%)
Swelling after exposure to cold	18 (9.0%)
Acrocyanosis	21 (10.5%)
Hyperhydrosis, severe	55 (22.5%)
Vasomotor instability	15 (7.5%)
(Noteworthy circulatory phenomena such as flushing, pallor, and sweating elsewhere than in the feet)	

*In spite of the care used in history taking, the authors doubt the specificity of this symptom, which is seldom, if ever, seen with vasoconstriction alone in the absence of occlusive disease. As pointed out in the discussion, these patients were infantry soldiers and complaints of structural origin were common.

Varying degrees of anxiety neurosis, including battle fatigue, were evident in fifty-one (25.5 per cent) of the group.

Heavy use of tobacco (more than twenty cigarettes daily) was admitted by 14 per cent of the men, moderate or slight use by 73 per cent, and nonuse by 13 per cent.

Alcoholic consumption was difficult to estimate. Overindulgence ordinarily becomes evident in a soldier's military record, and there were five (2.5 per cent) who, by this evidence, were heavy drinkers. One hundred seventeen (58.5 per cent) drank "moderate amounts socially," and seventy-eight (39 per cent) were total abstainers.

Weather: The dates of onset among the group were distributed as shown in Table II.

TABLE II

October, 1944	4 (2.0%)
November, 1944	118 (59.0%)
December, 1944	64 (32.0%)
January, 1945	1 (0.5%)
Not recorded	13 (7.5%)

During this period, our combat forces were deployed widely across Northern Europe. They were exposed to a great deal of rain, moderate cold, and occasional snow. Each soldier commented upon the moisture, and 186 stated that they were forced by circumstance either to crouch in foxholes partially filled with standing water or to wade and stand in deep mud. There were ninety men who mentioned wet snow falling on unfrozen ground. The exact temperature range is not available, but it can be inferred from descriptions and what is known of climatic conditions at that season that the so-called critical* freezing point for human flesh did not prevail to any significant extent.

Etiological Influence of Weather: The total group (200) was subdivided into three subgroups according to whether the onset of manifestations occurred before November 15, between November 15 and December 15, or after December 15, 1944. The so-called intrinsic factors, the peripheral circulatory symptoms, and the neurotic stigmas were compared, but there was no noteworthy difference in the incidence among them except for hyperhydrosis and psychoneurosis. These showed parallel progressive increase with the advancing season, each commencing with an incidence of around 20 per cent and ending at approximately 40 per cent.

A subdivision analysis was made of the ninety soldiers who mentioned snowfall during the period of exposure and compared with the 110 who did not. The initial finding of these groups is listed in Columns 4 and 5, respectively (Table III). The figures were considered essentially the same in both groups. The incidence of gangrene was the same.

Duration of Exposure: Prior to onset of the symptoms of foot trouble, duration of exposure is shown in Fig. 2. There was essentially no variation in the casualty incidence between one and fourteen days' exposure. Very few patients thought they had lived under unfavorable conditions for longer than fourteen days; 24 per cent developed symptoms within forty-eight hours.

Duration of Symptoms Before Reporting on Sick Call (Battalion Aid Station): Sixty-one soldiers (30.5 per cent) reported the condition of their feet within two days of the onset of symptoms; 93 (46.5 per cent), within three days; 117 (58.5 per cent), within four days; and 170 (85 per cent) within seven days. They were all taken off their feet and evacuated as soon as they reported. There were only a few (15 per cent) who failed to report before a week.

Early Findings (Battalion Aid Station): Very often the men had not inspected their feet between the time of onset of symptoms and reporting off duty. Sometimes battle conditions intervened, but it was also common knowledge that shoes, once removed, could not be replaced on rapidly swelling feet. A list of the early signs and symptoms commonly noted, with the numbers and percentages, affected by each, is shown in Table III.

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*According to Lewis,[9] flesh freezes between −2° and 0° C. (28.4° and 32° F.), a temperature not reached until the surrounding atmosphere is −4° to −10° C. (24.8° to 14°F.), provided the skin is dry and retains its natural oils. This margin of safety is a phenomenon known as supercooling and is governed by laws of heat conductivity. Moisture, apposition of metal, and moving currents of air are especially effective in abolishing it.

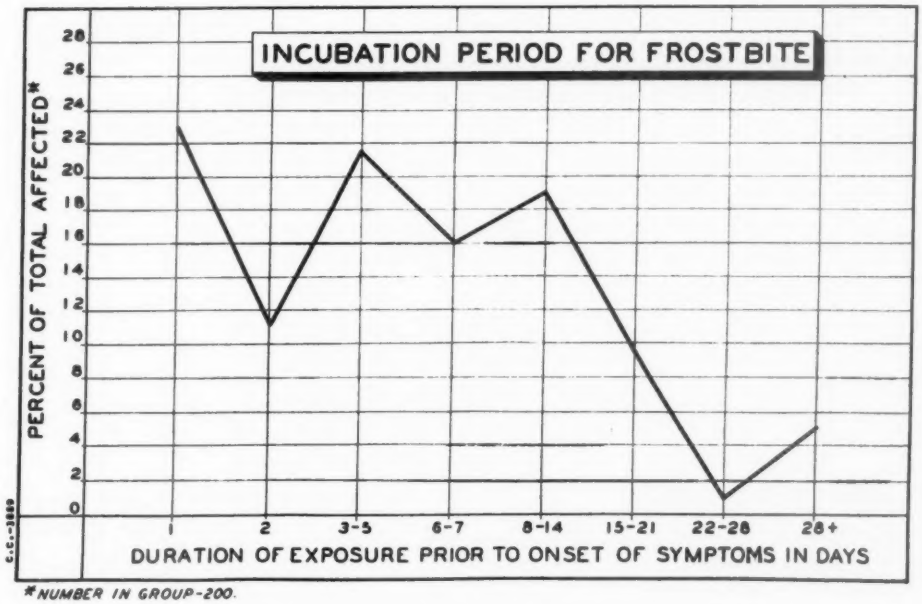

Fig. 2.—The duration of exposure prior to the onset of symptoms (that is, incubation period) is illustrated. It is apparent, other factors remaining the same, that if an individual survived exposure for two weeks or longer without developing symptons, he had a good chance of avoiding injury. The possible significance of the length of the exposure to the clinical syndrome developed is commented upon in the text.

TABLE III. EARLY FINDINGS NOTED AT BATTALION AID STATION

PHYSICAL SIGN	ENTIRE SAMPLE (200 CASES)	SEVERELY VASOSPASTIC TREATED WITH SYMPATHETIC BLOCK (62)	LESS VASOSPASTIC (138)	EXPOSURE ASSOCIATED WITH COLDER TEMPERATURE (SNOW) (90)	EXPOSURE AT HIGHER TEMPERATURE (NO SNOW) (110)
Swelling	149 (74.5%)	30 (48.4%)	119 (86.2%)	71 (78.8%)	93 (84.0%)
Redness	30 (15.0%)	5 (8.0%)	25 (18.0%)	16 (17.7%)	15 (13.6%)
Cyanosis	52 (26.0%)	14 (22.6%)	38 (27.5%)	30 (33.3%)	26 (23.6%)
Pallor	16 (8.0%)	8 (12.9%)	8 (5.8%)	4 (4.4%)	13 (11.7%)
Heat	6 (3.0%)	2 (3.2%)	4 (2.9%)	5 (5.5%)	2 (1.8%)
Coldness	17 (8.5%)	7 (11.3%)	10 (7.2%)	8 (8.8%)	8 (7.3%)
Numbness	71 (35.5%)	30 (48.4%)	41 (29.7%)	27 (30.0%)	30 (33.6%)
Blisters	12 (6.0%)	1 (1.6%)	11 (7.8%)	5 (5.5%)	13 (11.8%)
Pain	69 (34.5%)	17 (25.8%)	52 (37.6%)	30 (33.3%)	46 (41.7%)
Gangrene	7 (3.5%)	0	7 (5.0%)	3 (3.3%)	4 (3.6%)

When medical histories were taken at the 81st General Hospital, the earliest signs of frostbite observed by the patient at the first foot inspection following the onset of symptoms were recorded. These are tabulated with the number of patients affected by each sign. In Column 1, the figures for the group (200) as a whole are listed. Columns 2 and 3 and 4 and 5, respectively, represent two special rearrangements of the data to illustrate points of interest. As described in the text, certain individuals were more vasospastic than others; 62 such persons (Column 2) are

compared with 138 controls (Column 3). It was noted that there was a tendency for patients who were more severely vasospastic when studied at the general hospital to have had an early appearance of signs (that is, coldness, numbness, pallor), whereas the controls tended toward signs of inflammation, such as swelling, pain, and blisters.

A study to show the possible etiological effect of temperature during the incubation periods of frostbite is shown in Columns 4 and 5, respectively. In Column 4, there are 90 patients, who were exposed during presumably colder weather as indicated by snowfall, for comparison with 110 patients in Column 5, who were not exposed to snow. It is apparent from a comparison of the early signs that this factor had no significant effect upon the type of frostbite developed. Other more significant factors are discussed in the text.

Findings on Admission to the 81st General Hospital.—The temperature of the feet* was considered normal bilaterally in 77 patients (38.5 per cent); one foot was normal and one was cold in 5 (2.5 per cent); both feet were cold in 67 (33.5 per cent); one foot was cold and one was hot in 8 (4 per cent); both feet were hot in 41 (20.5 per cent); and one was hot and one normal in 2 (1 per cent).

The color of the feet was normal in 47 patients (43.5 per cent). There was rubor in 98 (49 per cent); blueness in 4 (2 per cent); and pallor in 31 (15.5 per cent).

The feet of 69 (34.5 per cent) of the group had some demonstrable edema remaining when they were admitted; 32 (16 per cent) had blisters; 44 (22 per cent) had excessive hyperhydrosis, and 163 (81.5 per cent) had well-marked hyperesthesia.

Pulsations of the dorsalis pedis arteries were palpable in both feet in 151 (75.5 per cent) patients. Pulsations were palpable on one side only in 18 (9 per cent), and completely absent in 31 (15.5 per cent).†

Pulsations could be palpated in both posterior tibial arteries of all of the 200 patients.

Seven (3.5 per cent) patients had superficial areas of gangrene (third degree) on the tips of the toes or at spots subjected to shoe pressure.

TREATMENT REGIME

When each patient arrived in the general hospital, treatment was prescribed according to individual indications.

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*Temperatures were estimated by the examiners by applying the backs of their hands directly to the skin. The dorsal surface of the hand, especially on the ulnar side, is more sensitive to temperature than the palmar surface. Since the temperature of the feet of so-called normal persons may vary widely and clinical estimates are necessarily inexact, whenever possible several examiners participated and groups of patients were tested concurrently. Temperature differences are more easily appreciated than absolute values.

†Since this paper was written, Silverman[11] has reported a study of the incidence of palpable pulsations in the dorsalis pedis and posterior tibial arteries of 1,014 healthy young soldiers, comparing the findings in Negro and white soldiers. Since our series contained only one Negro, these figures may be compared with his white group, among whom pulsations were absent in both dorsalis pedis arteries in 8.3 per cent; posterior tibials, 1 per cent; and, in one or more of the four sites, in over 13 per cent. There is no doubt in our minds that pulsations may be abolished by frostbite since they frequently appeared with treatment and acute vasodilatation induced by heat or nerve block.

In the presence of swelling, heat, and hyperemia, patients were kept in bed with their feet elevated* to a level slightly above the heart. Otherwise the bed was kept horizontal.

Trauma to injured tissues was carefully avoided and the feet were kept cool and dry. Artificial cooling was rarely necessary. The wards were Nissen huts heated by three charcoal burners spaced down the center. The heating was uneven and in winter the air at the ends of the ward and along its outer walls was always sufficiently cold if feet were uncovered.

As soon as gross edema subsided, exercise was commenced. Standard Buerger's exercises† were given, gradually at first, but rapidly increasing in duration and frequency, as tolerated. Early weight-bearing was encouraged and latrine privileges, a considerable incentive, was offered to those able to walk.

The treatment of complicating gangrene has been described elsewhere[4,6,8] and was not a feature of this study. Gangrenous areas, if superficial, together with blisters and occasional spots of deeply exfoliating skin, need special care as protection from trauma and infection, but this usually does not greatly delay the rehabilitation program.

With exercises and symptomatic treatment, daily improvement was usual. It progressed at different rates and to varying levels, but when it halted with evidences of marked persistent vasospasm, special vasodilatatory measures were added. Two such procedures were available. One was injection of lumbar sympathetic ganglia,‡ and the other, contrast whirlpool baths. As far as the present case group was concerned, sympathetic block was used selectively on those individuals with obdurate and severe peripheral vasospasm.

An active rehabilitation program was integrated carefully as a part of the treatment. As soon as weight-bearing was possible, shoes were fitted (usually several sizes larger than customarily worn by the patient) and walking was encouraged. Hikes and road marches were used to recondition the feet, and ability to tolerate these marches in winter weather formed an important criterion of progress and guided the ultimate disposition of the patient.

VASOSPASTICITY FROM FROSTBITE

As has been pointed out, vasodilation by sympathetic block was reserved for obdurate, severe cases of vasospasticity. A total of sixty-two patients were so treated one or more times. These patients were selected from the group by the degree of vasospasm which they presented, for, of course, some vasospastic reaction, as well as tissue death, was common to all. This group which was featured by marked vasospasm, was restudied and compared with the remaining 138 patients who were less vasospastic and who will be referred to as controls. The following points were of interest.

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*Special wooden elevators were constructed to slip under the mattress and lift the entire leg from the hip, with the knee slightly flexed. This kept the legs comfortable and was more practicable than elevation of the foot of the bed.

†A sergeant was appointed and specially trained to supervise execution.

‡The injection technique is described in standard tests on anesthesia. The second, third, and fourth lumbar ganglia were anesthetized with 1 per cent metycaine or procaine unilaterally or bilaterally, as required.

Age: Of the special group, 58 per cent were under 21 years of age, as compared with 34 per cent of the control group.

Combat Experience: The special group tended to have had less combat experience than the controls: 42 per cent as compared with 30 per cent, respectively.

Rank: There was no significant difference in military rank or assignment.

Duration of Exposure: Severely vasospastic feet tended to have had longer periods of exposure before symptoms were recognized. This was especially noteworthy among those who were exposed less than forty-eight hours before the onset of symptoms; the figures were 11 per cent as compared with 29 per cent for the control group.

Weather: Weather conditions during the period of exposure were not different in the two groups so far as could be learned by studying the incidence of snowfall and the dates of onset of frostbite.

The intervals between onset and evacuation, that is, cessation of weight-bearing, were likewise similar.

Past History: The incidence of earlier frostbite, as well as the incidence of pre-existing peripheral circulatory difficulties and anxiety neurosis, was the same in both groups.

Early Findings (Battalion Aid Station): The figures giving the incidence of the common earliest noted findings of the severely vasospastic feet and the control group are shown in Table III, where they may be compared with each other and with figures for the entire group. Pallor, coldness, and numbness were noteworthy among the special group, whereas swelling, hyperemia, heat, blisters, and pain were more marked among the control group. All seven patients who had gangrene were among the 138 controls.

Later Findings (81st General Hospital, on Admission): Coldness of the feet was a feature in 43.5 per cent of the patients who were later treated with sympathetic blocks as compared with 29 per cent of those who were not so treated. Pallor was more notable (26 per cent as compared with 11 per cent) and pulsations of the dorsalis pedis arteries were more commonly absent (39 per cent as compared with 5 per cent). There was some ruborous discoloration of the feet in approximately 50 per cent of the patients in both the special vasospastic and control groups. Bleb formation, swelling, redness, and heat had a similar incidence among the two groups at this stage. Both groups had greater than 80 per cent incidence of hyperesthesia.

RESULTS OF TREATMENT

Of the 200 soldiers in the total group only 45 (22.5 per cent)* were returned to duty; 21 returned to combat and 24 to limited duty. One hundred twenty-five

*These figures should be considered in the light of Theater policy during the early winter, when it was deciced not to congest hospitals and rehabilitation facilities with these patients. Later, the policy was reversed with consequent conservation of manpower.

(63 per cent) were returned to the United States because of persistent vasospasm, 7 (3.5 per cent) because of gangrene, and the remainder because of complicating neuropsychiatric conditions.

Of the 62 more severely vasospastic patients treated by paravertebral blocks, 4 (6.38 per cent) returned to limited duty and 58 were returned to the United States. Temporary relief of the vasospasm was obtained, but after a test period of activity in the rehabilitation unit with road marching and exposure to inclement weather, signs and symptoms recurred. There was no evidence, on the other hand, that this procedure had been harmful. Although our observations were too few and lacked sufficient control, it was our impression that the clinical course was not materially altered, one way or the other.

DISCUSSION

Of the several stages in the reaction of human flesh to cold stressed by Lewis,[9] two main effects are important from a clinical point of view: (1) vasoconstriction and relative anoxia of local tissues and (2) actual freezing with formation of ice crystals and mechanical disruption of cellular structure.

In the group under consideration, the pathologic mechanism was that of anoxia rather than freezing. Verbal weather reports from the patients themselves indicated that although ground snow was encountered by 45 per cent of the men in the group, the temperature was above the critical freezing point for flesh. Had actual freezing of tissue occurred, the incidence and extent of gangrene could have been expected to have been much greater, for it is well known that the formation of ice crystals in tissues, once begun, usually terminates in fourth degree damage.

Anoxia causes early increase in capillary permeability, exudation, and edema, followed by intense inflammatory hyperemia, when the part is exposed to warmth. The phase of vasodilatation is generally attributed to (1) the release of histamine-like substances from damaged tissues (so-called sterile inflammation), (2) direct injury to vessel walls, or (3) vasomotor paralysis secondary to injury of peripheral nerve fibers. Very possibly all three operate.

Whichever the mechanism, as soon as vasodilatation is established, anoxia is relieved and further tissue damage interrupted, provided, of course, the process has not already advanced so far that the tissues are swollen and congested with exudates.

Histologically, injured nongangrenous tissues have shown perivascular collections of cells dominantly lymphocytes, some polymorphonuclear leucocytes, and extravasated erythrocytes, with fibrinous exudate and blockage of the finer lymphatics.[12] Arterial walls may show intimal thickening, vacuolization of muscle fibers, and, at times, thromboses. Peripheral nerves usually show considerable change, predominantly degenerative. With healing, there is collagen and fibrous deposition, especially about nerve endings and vessels, sometimes extending deeply into the muscles. Stein and Dry,[13] studying soldier patients at a much later stage than our group, formed the opinion that "slow resolution of a chronic sterile inflammatory process with fibrosis within the tissues" is

adequate explanation for symptoms and findings. White and Warren[14] reported similar findings in immersion foot.

Clinically, we observed two dominant types of nongangrenous frostbite. Judging from histories and observations recorded in battalion aid stations, both commonly developed characteristic signs very early (Table III). Although gradation of severity and admixtures of findings were more common than pure examples, certain differential signs were noted.

The first type resembled severe acrocyanosis, with dusky, mottled, engorged tissues, cool to touch and sweating profusely. Pulsations in the dorsalis pedis arteries were palpable, sometimes full or increased. In the second type, the feet were waxy pale or cadaveric in appearance, sometimes with well-demarcated lines separating affected from normal tissues, cold to touch, and with little or no swelling. Patients with this type of lesion more commonly exhibited Raynaud-like phenomena of areas of pallor succeeded by hyperemia. In early stages, this second type was likely to be considered less severe because the feet had little or no early pain, swelling, or recognizable tissue damage. Actually, patients who presented the second type of involvement proved more resistent to treatment and rehabilitation, and fewer were returned to duty in the European Theater.

As reported, the incidence of severe vasospasm was higher in the youngest age group, among those who had had the least combat experience and who had been exposed to unfavorable conditions for longer incubation periods prior to onset of symptoms. The long incubation period with long-continued ischemia and tissue anoxia of relatively mild degree compatible with continued duty may, therefore, be singled out as an operating factor. Why it caused recognizably different effects than shorter periods of more intense anoxia is not known with certainty but the factors which govern so-called reactive vasodilatation, described previously, may be concerned. If, for instance, the hyperemic phase waits upon liberation of histamine-like substances, it is clear that a relatively severe degree of anoxia is, in turn, required for those substances to be liberated by cell dissolution. Lewis has called attention to the part these substances may have in the production of pain, a symptom which is most severe during the period of hyperemia. This spontaneously occurring pain should not be confused with various paresthesias which are more a feature of other stages. Cellular death, when grossly apparent, is, of course, gangrene. In the process of separation of gangrenous from viable tissues, there is commonly a well-marked zone of sterile inflammation. If the theory under discussion is true, it would account for the fact that severe persistent vasospasm was not a feature in such cases. Similarly, it would explain the apparent import of the observed early course and why the early occurrence of hyperemia, heat, pain, and swelling gave a better prognosis. It should be pointed out, however, that the same signs, presumably more intense in degree, could presage gangrene.

As far as the individual victim of frostbite is concerned, it is important to remember that biologic variations within the so-called normal range operate also in neurovascular reflexes. Certain individuals undoubtedly respond to stimuli more readily than others, as is evident from observations on Raynaud's syndrome which can occur in anatomically healthy extremities. Vasomotor

instability, evidenced by unusual flushing, pallor, coldness, and sweating, is frequently noted in emotionally labile persons. As pointed out in the data on prefrostbite symptoms, there was a large incidence of such stigmas, although the significance of intermittent claudication is questionable. The patients were infantrymen who are notoriously susceptible to cramps and pains in the legs and feet, which are structural in origin. The differentiation of the structural and nervous origin of symptoms is, therefore, not always easy. Twenty-two per cent had earlier frostbite, which clearly suggests unusual susceptibility in the group as a whole.

We believe the incidence of anxiety psychoneuroses has significance as an indication of susceptibility and that frostbite in such individuals may result from cumulative emotional and cold stimuli. In some instances, men had been evacuated primarily for battle fatigue; in others, for frostbite. Delayed or masked anxiety states which became manifest while the patient was in the hospital were not uncommon among casualties from all causes, but in our experience they occurred more frequently in those who had frostbite. We also noted that anxiety neuroses associated with frostbite were often severe and more resistant to active neuropsychiatric treatment by the pyschiatrist.

From our observations, it would be impossible to prove that occlusive arterial diseases were not a factor in the susceptibility of this group to frostbite. Ordinary clinical notation of color, temperature, and arterial pulsations were not adequate evidence in the presence of recent frostbite, and oscillometric and radiographic studies were not possible. However, careful search for evidence of vascular pathology in other parts of the system were made and were not found. There were no cases of diabetes mellitus and none had signs of thrombophlebitis. It was believed that parentage and habits (tobacco and alcohol) were very similar in this group and in comparable groups of military personnel without frostbite. And lastly, whereas such diseases are known to be important in older age groups,[1] a comparable incidence has not been reported among young persons.

Our data offered considerably less information concerning the role of extrinsic factors in frostbite (that is, foot care). These factors are generally recognized and well described elsewhere.[15] The difficulties and confusion in forward echelons has been mentioned in an earlier footnote in relation to nomenclature and awarding of the Purple Heart decoration. Under these circumstances, we considered the direct evidence in response to specific questions in the taking of medical histories to be unreliable. We did analyze data which were not suspect, and, as we have pointed out, frostbite apparently tended to affect the very young soldier, in combat for the first time, in preference to the older and more experienced infantryman who was exposed to the same unfavorable climate. The factors of length and kind of military experience prior to combat, rank, available objective evidences of training, native ability, and capacity to assume responsibility proved, on the other hand, so similar to their incidence in the rest of the Army as to discount their probable importance in the etiology of frostbite. Following the same line of thought, we came increasingly to discount the influence of willful self-neglect and carelessness in the ordinary sense and developed the

more charitable point of view that involuntary situations connected with combat, in susceptible individuals, accounted for the development of frostbite in a vast majority of instances.

SUMMARY

1. An analysis of 200 frostbite casualties, observed during the fall and winter of 1944-1945 in a Communication Zone general hospital in the European Theater of Operations, is reported.

2. Marked vasospasm of the feet was the chief morbid finding in this group.

3. The etiological factors concerned in frostbite are reviewed in the light of present observations, more especially in relation to the development of vasospasm. The following conclusions are reached:

(a) Faulty foot care (extrinsic factors) is an important factor among very youthful, "green" troops unused to taking care of themselves under combat conditions. There is no apparent correlation with individual characteristics of leadership, responsibility, and military education which ordinarily predicate military assignment and rank.

(b) Some individuals are especially susceptible to frostbite (intrinsic factors). This is shown by a high incidence of one or more earlier episodes of frostbite and by the number of patients who complained of symptoms suggestive of pre-existing poor circulation. The nature of the circulatory difficulties is considered. A few of the patients may have had early unrecognized or mildly obliterative arterial lesions while sensitive vasoconstrictor reflexes may have been concerned in others. The likely role of emotional stimuli re-enforcing cold among the latter group is discussed.

4. The clinical manifestations of nongangrenous frostbite are briefly described and two broad types differentiated. It was found that conditions conducive to relatively minor grades of local tissue anoxia, sustained during long periods, were likely to produce more severe and resistant vasospasm. The likely reasons for this are discussed.

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THE DIAGNOSIS OF TRICUSPID VALVE DISEASE

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THERE exists considerable divergence of opinion concerning the frequency and the diagnosis of lesions of the tricuspid valve. Opinions expressed by different authors not only have differed, but, at times, also have been diametrically opposed.[1-8] To a great extent these divergent points of view have been a reflection of the era in which the study was made.[3,10] An example of this fact is found in *Oxford Medicine*. In this book, MacKenzie,[9] who wrote the original chapter on the tricuspid valve, stated that organic lesions affecting this valve are rare and that in all his cardiologic experience he had found a presystolic tricuspid murmur in only three cases. On the other hand, Herrmann,[6] writing more recently on the same subject and in the same book, stated that these lesions are found in 25 to 30 per cent of all patients with chronic rheumatic mitral disease.

This disagreement can be explained, at least partially, by the fact that most authors speak of tricuspid lesions or tricuspid stenosis or tricuspid insufficiency without specifying exactly what they mean when they make these diagnostic distinctions. Some authors speak only of stenosis when there is fusion of the valve leaflets or thickening and sclerotic changes in the valve ring, even though valvular retraction and shortening of the chordae tendineae have also produced insufficiency. Other authors limit the diagnosis of stenosis to those lesions in which actual narrowing or an infundibular conformation of the valve orifice is the only peculiarity. Others give more attention to the clinical features of insufficiency and do not take into consideration the fact that almost invariably chronic regurgitation is accompanied by a concomitant stenosis. Garvin[11] believes that the presence of the symptomatology of regurgitation is sufficient to justify a diagnosis of stenosis.

To avoid the difficulties of nomenclature, it would be better to adopt the general name of tricuspid disease, as do Kerr and Morrison.[2] Because of the clinical nature of our paper and because of the importance of the symptoms of insufficiency, we have followed this course.

When we began our clinical studies, we accepted the opinion of other workers, that tricuspid lesions were not a common finding. Our clinical and necropsy studies, however, have taught us that lesions of the tricuspid valve are more frequent than is generally thought. The purpose of this paper is to present some of the observations and impressions that have come from our study of this interesting subject.

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MATERIAL AND METHODS

From September, 1944, to July, 1946, 250 autopsies were performed at the National Institute of Cardiology. Among these 250 patients, only six had normal hearts; of the 244 patients with cardiovascular disease, 147 (60.2 per cent) had rheumatic heart disease. Of the patients with rheumatic heart disease, seventy-three (49.6 per cent) had some degree of tricuspid involvement although only forty-nine (33.33 per cent of the total rheumatic series) had the type of deformity which produced tricuspid insufficiency. In eight cases (5.44 per cent) functional tricuspid insufficiency (without lesion of the valvular endocardium) was present.

Criteria for Diagnosis of Tricuspid Lesions.—Relative stenosis was deduced from the circumference of the valve, measured at the ring where the leaflets were not fused and measured at the free edge of the leaflets where fusion existed. The absolute figure of the valvular circumference was adjusted in accordance with the weight, height, age, and constitution of the subject. In addition to the circumference of the valve, the inlet and outlet tracts of the right ventricle were considered. Generally the outlet tract (the distance from the apex of the right ventricle to the pulmonary semilunar valves) is 10 to 15 mm. longer than the inlet tract (the distance from the tricuspid ring to the apex of the right ventricle). Enlargement of the ventricle nullifies or inverts this difference. Because of these various adjustments, even with absolute figures within normal limits, a *relative* stenosis may be present. Absolute or real stenosis is quite rare and, when present, is so obvious that there can be no doubt of its presence. It is interesting to observe that tricuspid stenosis does not produce auricular hypertrophy as does mitral stenosis.

Tricuspid insufficiency was deduced in two ways: (1) from the condition of the valves—their shortening or retraction, state of the edges and the length, thickening, and fusion of the chorda tendineae; and (2) from the effects of insufficiency—enlargement of the right ventricle, dilatation of the venae cavae, especially the inferior, condition of the liver, and particularly the state of the suprahepatic veins within the parenchyma.

Even though we recommend the general term tricuspid lesions for clinical use and insist that stenosis and insufficiency are combined in most instances, we have differentiated insufficiency and stenosis on the basis of pathologic findings. We have considered as true stenosis eleven of the forty-nine cases with organic tricuspid lesion (22.44 per cent) in which narrowing predominated over insufficiency from a strictly anatomic point of view. Our basis for asserting this was the evident fusion of the valves, the funnel type of orifice, or the marked decrease in the circumference of the valve ring.

We considered as cases of pure insufficiency those in which it was evident from the condition of the valves that regurgitation existed and predominated over the stenosis which was also present. Such insufficiency was found in twenty-eight (57 per cent) of the forty-nine cases with organic tricuspid lesions. In eleven cases (24 per cent) the evidences of both insufficiency and stenosis were so marked that it was considered proper to classify these as examples of double tricuspid lesions.

We found one isolated case of tricuspid valvulitis with insufficiency in a patient with bacterial endocarditis where autopsy did not show rheumatic heart disease. This completes a total of fifty cases of tricuspid disease of clinical importance.

With the exception of this one case of bacterial endocarditis in which valve damage was limited to the tricuspid valve, all of the remaining seventy-three cases of tricuspid valvulitis showed lesions of other valves. Of the fifty cases with important tricuspid lesions, only one (2 per cent), as we have said, presented a lesion of this valve alone; one (2 per cent) had a tricuspid lesion and mitral insufficiency; three (6 per cent) had a tricuspid lesion and pure mitral stenosis. In the other cases, the tricuspid lesions were associated with lesions of other valves as follows: double mitral lesion in eighteen cases (36 per cent), mitral and aortic lesions in twenty-seven cases (54 per cent), and, in one case, already cited, lesions of the other three valves (aortic, mitral, and pulmonary).

The eight cases of functional insufficiency of the tricuspid valve were accompanied by the following lesions which explained right ventricle dilatation: in five, the tricuspid lesion was accompanied by a double mitral lesion; in two, double mitral and aortic lesions; and, in one, by double aortic lesion.

In the fifty cases diagnosed as organic tricuspid lesion, twenty-four presented pulmonary infarcts (48 per cent). Five cases presented phenomena of thrombosis; in two the thrombus was located in the body of the right auricle (both patients had pulmonary infarcts) and in three the thrombus was in the right auricular appendix (one of these patients had pulmonary infarction). In eleven cases the lesions were accompanied by different types of pericarditis.

ANALYSIS OF SIGNS AND SYMPTOMS

Age.—The average age of fifty patients with tricuspid disease was 24 years. The minimum age was 9 years and the maximum age, 69 years.

Sex.—This series of fifty patients was composed of thirty-four women (68 per cent) and sixteen men (32 per cent).

Duration.—The average duration of the disease from the appearance of symptoms until death was judged to be sixty-four months.

Accuracy of Diagnosis.—The clinical diagnosis of tricuspid disease was proved by necropsy in seventeen (34 per cent) of the fifty patients.

Dyspnea.—Dyspnea on exertion was present in almost all patients. The histories of only two patients (4 per cent) indicated that this symptom was absent. Dyspnea in the supine position was stated to be present in thirty patients (60 per cent). It was apparently not present in twelve patients (24 per cent); the symptom was doubtful in eight patients (16 per cent). In three of the thirty patients, this symptom was present toward the end of illness; in three more patients, it was stated to be present at some time during the course of illness but was not present at the time of death.

Paroxysmal dyspnea was not an outstanding finding. This symptom was absent in thirty-six patients (72 per cent) and in three patients its existence was doubtful. Six patients (12 per cent) had episodes of acute pulmonary edema. Five additional patients (10 per cent) had something approaching pulmonary edema, but the data in the histories were not sufficient to justify a positive diagnosis.

Cough.—This symptom was absent in fifteen patients (30 per cent) and present in thirty-five patients (70 per cent). Fourteen patients (28 per cent) had hemoptysis. In six of these (12 per cent) the bloody expectoration was explained by pulmonary infarction, and in two (4 per cent), by pneumonia. In only six patients (12 per cent) could the hemoptysis be related to pulmonary congestion alone.

Cyanosis.—This sign was positive in twenty-eight patients (56 per cent). In seven of these patients (14 per cent) cyanosis was quite intense, in nine (18 per cent) it was of medium intensity, and in twelve (24 per cent) it was slight.

Color of the Skin.—Pallor was present in six patients (12 per cent), ashy pallor in twenty patients (40 per cent), pallor with cyanosis in eight patients (16 per cent), pallor with slight jaundice in four patients (8 per cent), pallor with cyanosis and slight jaundice in four patients (8 per cent), and marked jaundice in one patient (2 per cent).

Venous Distention.—This sign was present in the veins of the neck in forty-two patients (84 per cent). In eighteen of these patients (36 per cent) it was marked, in fifteen (30 per cent) it was of medium degree, and in ten patients (20 per cent) it was considered to be slight. Marked edema of the face was present in only six patients.

Venous pressure in the upper limbs was determined in thirty patients, in some of whom the procedure was repeated several times. The lowest venous pressure was 40 mm. H_2O, the highest, 240 mm. H_2O, and the average, 149 mm. of water.

Circulation time was determined by the decholin method in thirty patients. The minimum was 9 seconds, the maximum, 48 seconds, and the average, 26 seconds.

Ascites of varying degree was present in twenty-four patients (48 per cent). Edema was present in forty-two patients (84 per cent). In eight patients edema was generalized; in four it involved the lower limbs and face; in three it involved only the face (there were no signs of kidney disease); and in twenty-seven (54 per cent), only the lower limbs were involved.

Venous Pulse.—This sign was present in neck veins in eighteen patients (36 per cent). In four patients with marked jugular distention the venous pulse became more apparent in the sitting position and decreased with increase of the distention of the jugular vein brought about by assuming the prone position. The segment of the vein in which the pulse could be seen extended higher in the neck in decubitus than in the sitting position. This peculiarity has been described by White in patients with cor pulmonale and observed by Rivero Carvallo[25] in patients with tricuspid regurgitation.

Spontaneous Liver Pain.—Liver pain of variable intensity was a constant finding. Pulsation of the liver was a less frequent finding. Nine patients (18 per cent) developed intense paroxysmal pain in the epigastrium or right hypochondrium which radiated to the posterior aspect of the thorax and, less frequently, to the shoulder. These episodes of intense pain lasted from a few hours to several days and were frequently accompanied by vomiting.

Vomiting.—The appearance of vomiting not related to digitalis intoxication was a common finding (fourteen patients, 28 per cent). Often the history of patients with this symptom indicated that the vomiting was repeated in crises upon several occasions.

The Liver.—Hepatomegaly was a constant finding in all patients. In four patients (8 per cent) the liver was palpable only 1 to 4 cm. below the costal border in the midclavicular line. In all others, the liver extended more than 5 cm., and in two patients, 16 cm. below the costal border.

There was no mention of the consistency of the liver in seventeen patients. In the remaining thirty-three patients, consistency was increased in thirty (90.9 per cent), while no increase in consistency was noticed in three (9.1 per cent). Tenderness of the liver was present in forty-seven patients (94 per cent). Pulsation of the liver was studied in twenty-one patients (42 per cent). The sign was present in sixteen and absent in five patients. The function of the liver was studied in only twelve patients. In three (25 per cent) the function of the liver was found to be normal, and in nine patients (75 per cent), functional insufficiency was found.

In these nine the bromsulfalein test (Greene technique) showed a fixation of the substance in the liver of from 70 to 90 per cent, with an average of 82 per cent (normal, 95 to 100 per cent). Ten to 30 per cent of the dye was present in the blood: the average was 18 per cent (normal, 0 to 5 per cent). In these nine patients the van den Bergh test (Jendrassik-Czike method) gave positive results. The prothrombin index was studied in five patients. In three of these the index was decreased.

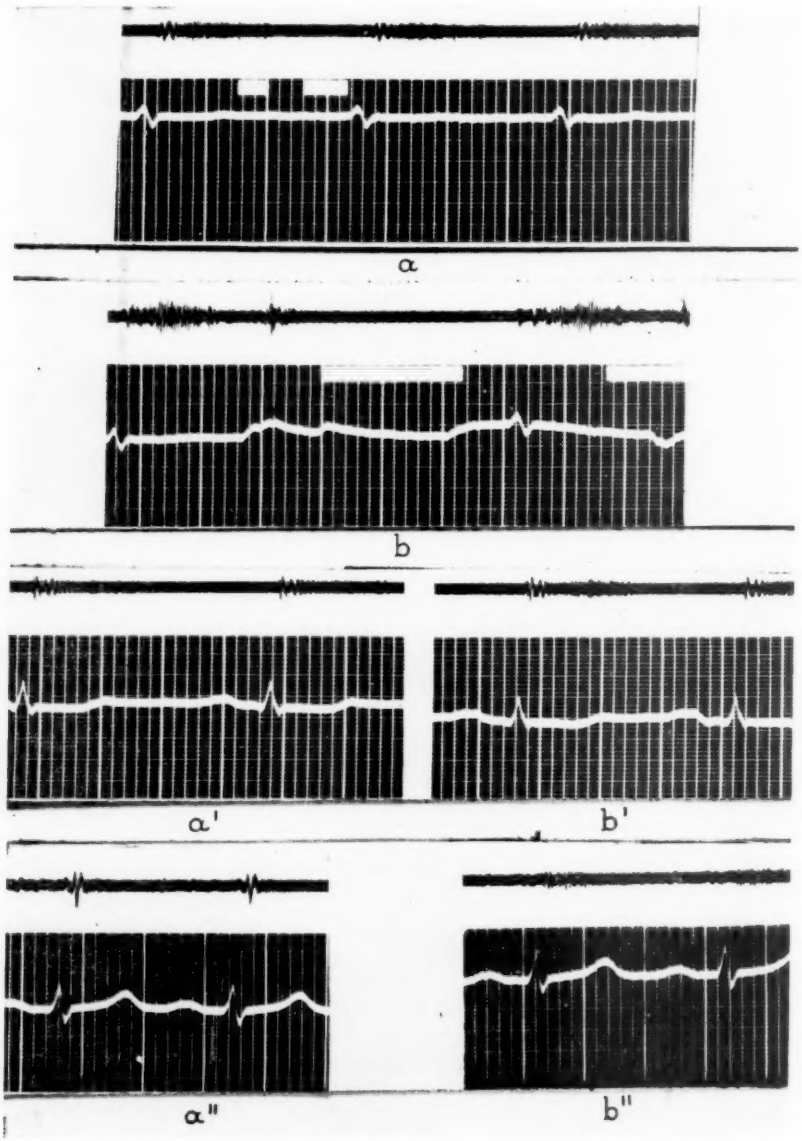

Fig. 1.—Phonocardiograms at the tricuspid area. In *a*, *a'*, and *a''*, during postexpiratory apnea: in *b*, *b'*, and *b''*, during postinspiratory apnea. Observe in *b*, *b'*, and *b''* the increase of the intensity of the systolic murmur when compared with *a*, *a'*, and *a''*.

Auscultation.—In seventeen patients (34 per cent) a tricuspid systolic murmur was identified. In eight patients the murmurs were identified by their acoustic characteristics, which differed from those of the concomitant mitral murmur. No special methods were employed.

In the other nine patients the method described by Rivero Carvallo[25] was used in order to identify the tricuspid origin of the murmur. This method consists in auscultation in postinspiratory and postexpiratory apnea.

Applying Levine's classification, the murmur was considered to be grade 1 in three patients, grade 2 in eight patients, grade 3 in five patients, and grade 4 in one patient. The murmur was highly pitched in all but one patient. It was more or less harsh ("*en jet de vapaeur*") in all but two patients, in whom it was musical. In twelve patients the murmur was transmitted toward the hepatic area and the region contiguous to the tricuspid area. In one patient the murmur could be heard at the apex. The first sound was absent in nine patients.

In ten patients the characteristics of the murmur were studied successively in postinspiratory and postexpiratory apnea (Fig. 1). In nine of these (90 per cent), increase in the intensity of the murmur over the tricuspid focus and an increase in the area over which it was transmitted occurred during postinspiratory apnea (Fig. 1). The murmur also became high pitched.

Electrocardiographic Findings.—Electrocardiograms were studied in forty-four patients. Auricular fibrillation was present in thirteen patients (29.5 per cent).

In thirty-one patients who did not have auricular fibrillation, the features of the P wave were analyzed in the three standard leads, the three limb potentials, and the six precordial leads (Wilson's method). The P wave was abnormal in every instance, being notched in twenty-seven patients and slurred in four.

The duration of the P wave was at least 0.10 second in twenty-five patients (80.5 per cent) and less than 0.10 second in six (19.5 per cent). The duration in the patient with an isolated tricuspid lesion was 0.08 second.

The mean manifest axis of P ($\hat{A}_P$) fell between +60 and +90 degrees (isoelectric, diphasic, or negative P in V_L, positive in V_F and standard leads) in sixteen patients (51.6 per cent), including the patient with an isolated tricuspid lesion whose $\hat{A}_P$ was situated at +75 degrees. In nine patients (29 per cent) the $\hat{A}_P$ fell between 0 and +60 degrees (P positive in V_L and positive, isoelectric, or diphasic in V_F). In six patients (19.4 per cent) the $\hat{A}_P$ fell between 0 and +60 degrees (P positive in V_L and negative in V_F). The average $\hat{A}_P$ in all patients studied was +45 degrees. In six patients who were studied electrocardiographically on several occasions, a right deviation of $\hat{A}_P$ was observed in the course of disease and reached 20, 30, 45, 50, and 100 degrees, respectively.

In the precordial leads, P was diphasic in V_1, V_2, and, in a few cases, in V_3 in all but one patient. Tracings made in the patient with isolated tricuspid disease are shown in Fig. 2.

The mean manifest axis of QRS ($\hat{A}_{QRS}$) deviated toward the right (between +90 and +150 degrees) in forty-one patients (93.2 per cent). The average $\hat{A}_{QRS}$ was +103 degrees; in the patient with isolated tricuspid valvulitis $\hat{A}_{QRS}$ fell at +105 degrees. In three patients $\hat{A}_{QRS}$ fell between 0 and +90 degrees; the average $\hat{A}_{QRS}$ was +99 degrees.

The mean manifest axis of T ($\hat{A}_T$) was determined in twenty-two patients whose electrocardiograms showed no alteration of the S-T segment and no influence of digitalis upon the T wave. In eleven patients (50 per cent) $\hat{A}_T$ was between 0 and −90 degrees; in the patient with pure tricuspid disease $\hat{A}_T$ was 0 degree. The average $\hat{A}_T$ of the group was −28 degrees. In the remaining eleven patients (50 per cent) $\hat{A}_T$ fell between 0 and +90 degrees, with an average of +40 degrees. The average $\hat{A}_T$ for all twenty-two patients was +12 degrees.

The time of onset of the intrinsic deflection in V_1 and V_2 was 0.04 second or more in twenty-eight patients (63.63 per cent); in the remaining sixteen patients the time was less than 0.04 second. In the patient with the isolated lesion the time was 0.07 second in V_2 and 0.06 second in V_1 (Fig. 2). The average time registered in V_1 and V_2 in all patients was 0.041 second, the maximum being 0.07 second and the minimum, 0.01 second.

Certain other findings are of interest. On several occasions we found a negative T wave in the right or left or in all precordial leads and a deep S wave in V_5 and V_6. Because of the small number of cases, no attempt is made to analyze these findings.

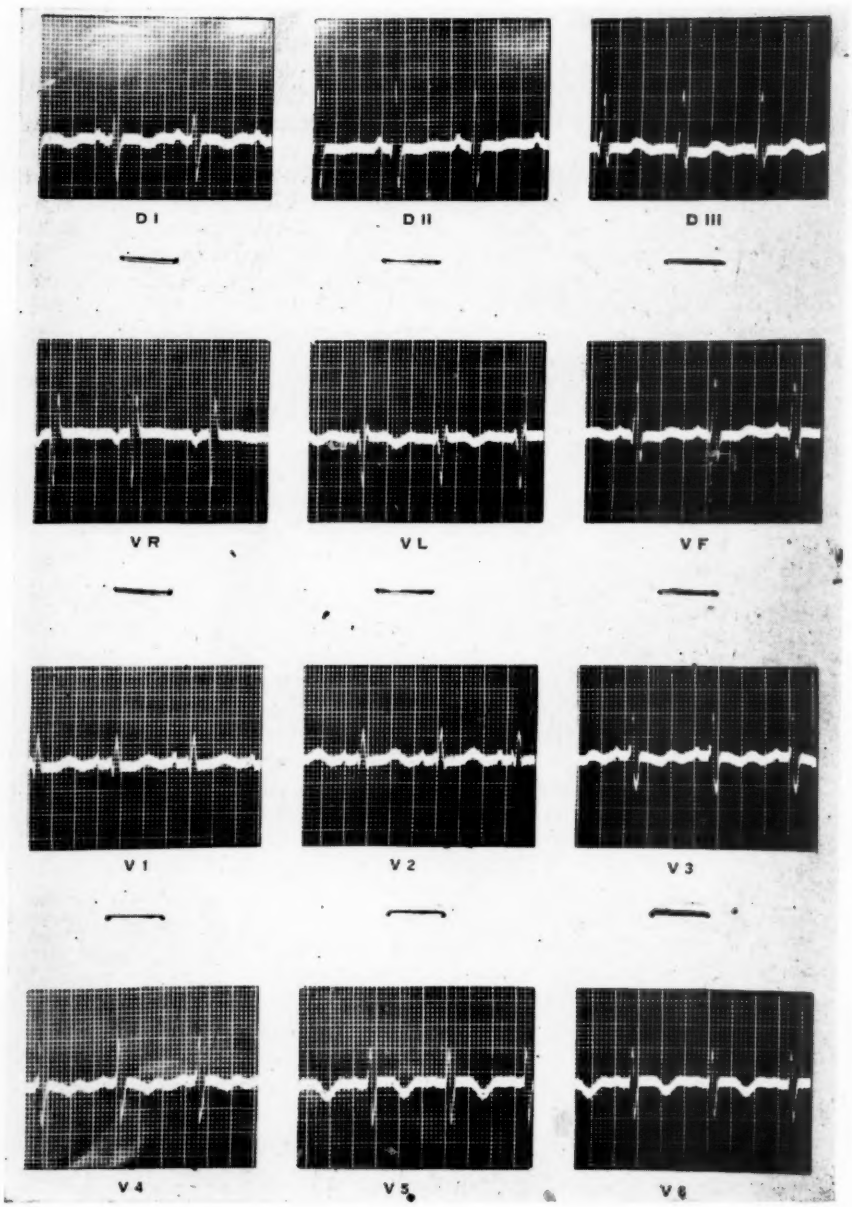

Fig. 2.—Tricuspid insufficiency without other valvular lesions.

*X-ray Signs.**—The x-ray findings must be divided in two different groups: dynamic and static signs. Since the majority of patients had aortic insufficiency, the dynamic signs characteristic of this condition were present. In two patients, however, who had mitral and tricuspid lesions without aortic involvement, dynamics of the aortic type were observed. In the patient

*We are indebted to Dr. N. Dorbecker, Chief of the X-Ray Department, for his valuable suggestions and criticisms.

with isolated tricuspid involvement whose blood pressure was 110/0, the aortic type of phenomena was observed; it is possible that some other lesion in the peripheral circulation (arteriovenous fistula?) capable of producing such phenomena was present.

The static findings were as follows: In twenty-two of the forty-five patients (48.88 per cent) the right atrium was clearly increased in volume (grades 2 to 4). In the patient with pure tricuspid disease the enlargement was considered to be grade 3. In twenty-five of the forty-five patients (55.55 per cent) the left atrium was enlaged (grades 2 to 4). In these twenty-five patients the tricuspid disease coexisted with mitral stenosis. The patient with pure tricuspid disease did not show left atrium enlargement. In twenty of the forty-five patients (44.44 per cent) the right ventricle was enlarged (grades 2 to 4). The patient with isolated tricuspid disease had grade 3 enlargement.

The pulmonary arch showed definite but not extreme prominence in seventeen patients (including the patient with tricuspid disease); a more prominent arch was present in seven patients. The hilar shadows were accentuated in thirty-three (73.33 per cent) patients. A double contour of the right cardiac silhouette was present in nine patients (17.17 per cent). There were five additional patients in whom a visible right bronchus simulated a double contour. The esophagus was not deviated to the left in any patient. The lungs were normal in seven patients (15.55 per cent), despite the fact that all had serious mitral disease. In eight patients the superior vena cava was dilated in anteroposterior and right oblique positions.

In patients in whom kymographic studies were made, no atrial contour indentations of ventricular type were observed, although the auricles showed increased pulsations.

COMMENT

Our experience with cardiac patients, particularly those with chronic rheumatic disease, has convinced us that the effort to determine with precision the number of valves affected and the degree and type of involvement is of more than academic importance. It is our conviction that if the condition of the myocardium is fundamental in the production of cardiac failure, then disease of the valves constitutes a prime factor in producing the failure of the myocardium and is the determining cause of the type of heart failure which develops in the course of chronic valvulitis. We feel, therefore, that the concepts of the English school are not altogether correct. MacKenzie and Lewis emphasized the lack of importance of valvular lesions. This is the exact antithesis of the teaching of Levine,[12] who maintains that valvular lesions are of highest importance in chronic rheumatic heart disease and are more important than the myocardium as a primary cause of cardiac insufficiency in patients with rheumatic heart disease, except when acute carditis is present. We believe that Levine's opinion justifies every effort to diagnose valvular lesions with precision.

Although our autopsy experience had shown that clinical study failed to recognize many tricuspid lesions, nevertheless, we were surprised that in a large series of patients with rheumatic heart disease, 33.3 per cent had sufficient involvement of the tricuspid valve to make diagnosis possible. This figure can be raised to 50 per cent if we include the patients with slight valvular endocarditis which did not deform the valve and which did not cause functional derangement. (In the latter group, diagnosis is impossible.)

This incidence (33.3 per cent) is higher than that published by some other authors.[6,7,9,11] Combs (cited by Cooke and White[13]), however, gives a higher incidence: thirty-five of ninety-seven patients with rheumatic heart disease. Von Glahn in 1927 (cited by White and Cooke[13]) found forty-one examples of

tricuspid involvement in 109 rheumatic patients. Libman found an incidence of 60 per cent in eighteen patients. Thayer (1929) found an incidence of 44 per cent.

Herrmann has stated[6] that the tricuspid valve is involved in 25 to 30 per cent of patients with chronic rheumatic valvular disease (we found 49 per cent) and that in two-thirds of such patients there is only slight valvular damage. Bland, Jones, and White[14] found tricuspid lesions in thirty-one of 100 rheumatic patients. In thirty of 217 cases of rheumatic heart disease, White and Cooke[13] found the valvular lesion sufficiently marked to give clinical signs. Garvin[11] found tricuspid involvement in 36.1 per cent of 119 rheumatic patients. In 10.9 per cent the involvement was sufficiently advanced to produce an actual stenosis.

It is obvious that the figures we present, based on autopsy findings, pertain, by definition, to seriously ill patients with advanced disease and, consequently, do not give a true picture of the clinical frequency of these lesions. However, the figures given by other authors were also obtained from autopsy findings. Our study finds justification in the fact that one of every three patients with advanced rheumatic heart disease has lesions in the tricuspid valve.

So rare is the isolated tricuspid lesion that we found it in only one case and it was not rheumatic. It was an extraordinary case for many reasons. In all other cases other valves were involved. In 44 per cent the tricuspid lesion was associated with mitral lesions (stenosis, insufficiency, double lesions), in 54 per cent with mitral and aortic lesions, but only in 2 per cent with lesions of the other three valves.

This coincidence with other better known lesions of clearer symptomatology explains in part why tricuspid damage is so often unrecognized. This association of tricuspid lesions with other valvular lesions is so frequent that Shattuck, quoted by Futcher,[10] proposed that the diagnosis of tricuspid disease be made on the basis of this association: "Whether or not your hear a presystolic murmur of tricuspid stenosis it can surely be diagnosed, if the patient is a woman with rheumatic antecedents, *if she has mitral and possibly aortic stenosis* and gives evidence of prolonged and recurring venous stasis."

The clinical diagnosis of the tricuspid lesion was correctly made in 34 per cent of our series. Even though it is a low percentage, it is nevertheless higher than that found in other studies we have been able to consult and serves to emphasize how rarely the diagnosis is made.

There is nothing unusual in respect to the age of our patients. The age corresponds to that found by other authors and is about the same as that obtained by Cortés and Villarreal[35] in rheumatic patients with other types of heart lesions. The same can be said concerning the role of sex, since mitral disease also predominates in women. The average duration of life in the patients of our series differs decidedly from that given by Levine. This makes us doubt the compensating effect of the tricuspid lesion and its action in prolonging life.

Dyspnea was an almost constant finding, being absent in only 4 per cent of the patients. Nevertheless, its intensity was of a lesser degree than is commonly found in patients with rheumatic lesions who are as seriously ill as the patients of our series but who do not have tricuspid involvement. This suggests that the reduction of the output toward the pulmonary artery due to the tri-

cuspid lesion exempts the lungs, to some extent, from marked congestion, such as would be produced if the effects of the associated lesions were not neutralized in part by the tricuspid lesion, which acts as a sort of "safety valve."

The low incidence of paroxysmal dyspnea was remarkable. Dyspnea of decubitus was present in 60 per cent of the cases but absent in 40 per cent of seriously ill patients with mitral disease. This interesting finding was very often useful in diagnosis. Involvement of the tricuspid valve is suggested when a cyanotic patient with distended veins, at times with edema and ascites, is able to maintain recumbency without discomfort. This clinical feature, we discovered later, had been described by Duroziez in 1868.

Cough was not a constant finding. It was absent in 30 per cent of the patients. This is also an unusual finding in patients with severe cardiac insufficiency. Its absence has the same significance as the inconstancy of dyspnea.

Cyanosis, on the other hand, was found in varying degree in the majority of patients (56 per cent). It is fundamentally caused by the stasis and therefore belongs to the peripheral type of cyanosis.

The combination of pallor, cyanosis, and jaundice was present in only 8 per cent of our series. This combination gives the patient a very special appearance, as if he were under a mercury vapor lamp. This peculiar color was considered to be very characteristic by Shattuck. Wearn regarded it as a pathognomonic sign. Christian referred to it repeatedly.[18-20] We have observed this peculiar color, which might be called "Shattuck's sign," and have found it in association with tricuspid disease in some patients. However, the low percentage incidence in our series suggests that it is not a very common finding in tricuspid disease. Nor is it pathognomonic of tricuspid disease because it also may be found in other clinical conditions, such as constrictive pericarditis and sclerosis of the mediastinum.

Venous distention is one of the most important clinical signs because it is both frequent and outstanding. It was particularly constant in the neck veins where it was found, in greater or lesser degree, in 86 per cent of our patients. The presence of distended cervical or even facial veins in a patient lying in bed without evidence of dyspnea should suggest involvement of the tricuspid valve if one can eliminate certain other conditions, such as constrictive pericarditis, in which the venous return into the right auricle is impaired. Jugular distention often gives these patients a particular sensation of plethora and cervical pressure that is very uncomfortable.

The typical jugular pulsation was mentioned in the histories of only eighteen patients (36 per cent) of our series. In the remaining patients it is possible the sign was overlooked. It is also possible that the sign was absent. Absence of pulsation can occur[5] but is difficult to explain. The decrease of the pulse in decubitus, also noted by other authors, we attribute to the permanent increase of pressure within the vessel, which, with a lesser degree of filling, permits wider variations of pressure in the different phases of the cardiac cycle and which, in turn, determines wider excursions of the vessel during systole. This amplitude of the jugular pulse, its occurrence in systole, and the frequent coincidence of

aortic insufficiency make it quite easy to confuse a venous pulse with the Corrigan type of pulse in the carotid arteries.[18]

In the phlebogram it has been shown that the jugular and other venous pulses[21] are characteristic and give an exaggerated C wave without the sustained waves of stasis that join the C and V waves. White and Cooke[18] have described a type of deep jugular pulse, seen in the phlebogram, which they believe to be a pathognomonic sign of tricuspid disease, when it is associated with chronic and constant congestion of the systemic veins. In the phlebogram a wide wave of stasis is observed in the rapidly ascending limb of the systolic evaluation. We did not find this wave.

The venous pulse in the forearm which Levine[3] has called the most constant and suggestive clinical finding, and to which MacMillan has attached so much value, was not mentioned in the histories of any of our patients who were studied at necrospy. One of us looked for it carefully in thirty other patients who were not autopsied and found it present in only four patients.

Edema was almost as common as jugular distention. It was found in 84 per cent of our series. This is readily explained since these patients had typical congestive heart failure. In 48 per cent there was ascites, although in only 16 per cent was generalized edema present. This is also easily explained on the basis of portal hypertension. In 100 per cent of the patients hepatomegaly was present, and in 90.9 per cent the consistency of the organ was increased.

Hepatomegaly is of great importance in the diagnosis of tricuspid disease because it is so common and its pathogenesis so well understood. This carries such clinical weight that in a patient who has recovered from heart failure but has a persistently large liver we can suspect participation of the tricuspid valve among the valvular lesions. Hepatojugular *reflux* was not mentioned in any of the histories. Together with physical modifications of the liver, we found, in the cases so studied, a functional deficiency proved by the different tests, particularly the test of pigmentary function. This explains the special color of these patients. Crises of hepatic pain and frequent vomiting, not related to digitalis intoxication, were observed more often in combined mitral and tricuspid disease than in mitral disease alone. In addition to actual pain, a sensation of heaviness and fullness in the upper part of the abdomen was a common symptom in our series of patients.

A *seesaw movement* involving the apex and xiphoid area (Fig. 3) such as was described by Lang and by Dressler,[22-23] was seen in only a few patients. In more patients we found a *systolic heave of the lower part of the sternum* produced by hypertrophy of the right cavities.

Undoubtedly the presence of a systolic murmur in the tricuspid region supercedes in importance all other signs and constitutes the strongest basis for the diagnosis of tricuspid disease. The proof of this lies in the fact that the seventeen patients (34 per cent) in whom the diagnosis was correctly made all had a systolic murmur. It is not always easy to detect this murmur because of the constant coincidence of a mitral murmur. In eight patients, however, both murmurs could be clearly recognized and differentiated by differences in intensity and timbre and by the location at which each murmur could be heard best. In the

other patients, the recognition of the murmur required the employment of the special technique which has been described.[25] This, we believe, has a great clinical value.

The intensity of a systolic murmur heard over the tricuspid region is increased during a deep, held inspiration only when the murmur originates in the tricuspid valve. The increase in intensity is explained by the increase of the negative intrathoracic pressure during inspiration which increases the blood flow toward the venae cavae and augments the blood velocity. This dynamic factor necessarily produces an increase of the pre-existing organic murmur.

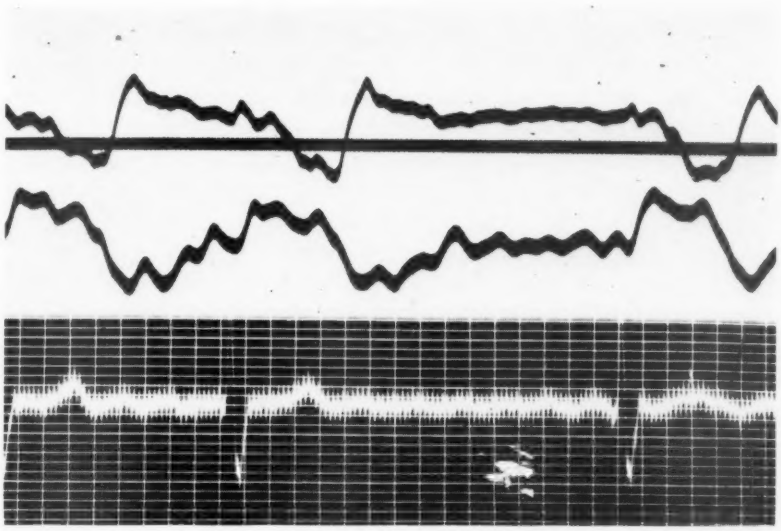

Fig. 3.—Upper tracing, apex cardiogram. Middle tracing, xiphoid cardiogram. Lower tracing, electrocardiogram, Lead II.

Interposition of the expanded lung between the heart and the point of auscultation does not affect tricuspid murmurs, since these murmurs are heard at a point where no pulmonary tissue exists. The descent of the diaphragm in inspiration tends to bring the portion of the heart in which the murmur originates nearer to the point at which the stethoscope is placed.

In contrast, a systolic mitral murmur is generally not intensified and may even be diminished during a deep, held inspiration. The increase of the output of the right side of the heart that follows inspiration does not affect the left side of the heart in the same abrupt and direct way in which increased venous filling affects the right heart because of the interposition of the lungs. Furthermore, inspiration, by increasing the volume of the pulmonary appendage located between the apex of the heart and the chest wall, can decrease the intensity of the acoustic phenomena which occur at the apical region.

In general, this method was useful, and when it gave clearly positive results, it was decisive in the diagnosis. Up to the present, in all autopsied patients in

whom the Rivero Carvallo sign had been positive, a tricuspid lesion was found. We believe an early diagnosis can be made in 80 per cent of patients with tricuspid involvement, even though late manifestations of increased venous pressure, which would facilitate diagnosis, may not have appeared.

The electrocardiographic signs found permit us to conclude that this method of study can, at times, help in the elaboration of the diagnosis or give a hint of the diagnosis which can be reached by other means. Here again one meets the difficulty created by the presence of concomitant mitral lesions which alone can alter the electrocardiogram in a similar but not in an identical way. The morphologic alterations and alteration of the voltage of the P waves can be found in pure mitral valvulitis, in the pure tricuspid valvulitis, and in the associated forms.

However, an average deviation of the axis of the P wave toward the right (above 60 degrees) in a patient with mitral disease who does not show clinical evidence of associated cor pulmonale strongly suggests the existence of a concomitant tricuspid lesion. Unfortunately, a large number of patients with tricuspid involvement have auricular fibrillation (29.5 per cent in our series) which prevents the use of this sign. Furthermore, it was positive in only 51.6 per cent of our patients. It is well known that mitral diseases, by creating left auricular hypertrophy, displace $\hat{A}_P$ to the left with the result that the great majority of these patients have an average P axis deviation to the left of 58 degrees. However, there are exceptions to this rule and so the finding of $\hat{A}_P$ to the right of this limit in mitral disease, even without added cor pulmonale, if not pathognomonic, is at least suggestive of a tricuspid lesion. Theoretically, the observation in serial tracings of progressive deviation, more or less rapidly, of $\hat{A}_P$ toward the right in the course of active rheumatic disease, as we have observed several times, is of more diagnostic value.

A diphasic P wave is commonly observed in precordial leads of patients with left auricular hypertrophy which is frequently a result of mitral disease. Such diphasic P waves are also found in patients with tricuspid disease; we were able to verify this in one case of pure tricuspid disease. This sign, which has recently been described by Ellis and Brown,[40] we do not believe to be of value because of the common association of tricuspid and mitral valve disease.

The deviation of the $\hat{A}_{QRS}$ to the right and of $\hat{A}_T$ to the left, often found in our series, commonly occurs in patients with mitral disease alone and for this reason does not have diagnostic importance. On the other hand, a delayed onset of the intrinsic deflection in V_1 and V_2 of more than 0.04 second, which we found in 62.62 per cent of our patients (including the patient with pure tricuspid disease), seems to have more diagnostic importance. To evaluate this sign correctly it is necessary to determine the frequency of its occurrence in other conditions, such as pulmonary stenosis, arteriosclerosis, or pulmonary arteritis. Pellon, who was the first to call attention to the intrinsic deflection in the right precordial leads and who is now investigating this subject, has the impression that whenever there is a delay in the onset of the intrinsic deflection in V_1 and V_2 in a patient with rheumatic heart disease, there exists a tricuspid lesion, if right bundle branch block is not present.

The dynamic signs revealed by radiologic study of several of our patients with mitral and aortic disease can confuse the diagnosis. In patients with aortic, mitral, and tricuspid lesions, dynamic pulsations of the aortic type have an obvious explanation, but such dynamic pulsations found in those without aortic lesions may have different causes: (1) A dynamic pulsation of the apex may result when the left border of the cardiac contour is formed by a greatly hypertrophied right ventricle, the movements of which are influenced by tricuspid regurgitation. (2) Tricuspid insufficiency may cause dilatation and systolic pulsation of the superior vena cava. In the right anterior oblique position, the superposition of the shadows of the cava and the aorta give the impression of a single arterial vessel which is widened and hyperpulsatile. Careful x-ray study of the superior vena cava from various angles will lead to the correct diagnosis.

The x-ray study of the diaphragm in several patients with clinical diagnosis of tricuspid lesion has brought to our attention a useful sign: the diaphragmatic pulse, which is really the hepatic pulsation transmitted to the diaphragm.

Hypertrophy of the right auricle was frequent. Quite often hypertrophy of the left auricle was also present. When the double contour of the right auricular shadow was real, we could explain it by the *incomplete superposition* of the auricles whose enlargement was unequal. This idea is confirmed by the observation of the angiocardiographic films made by Dorbecker, employing the special technique of Celis.[39] This x-ray image, not constant, we believed to be of diagnostic value in tricuspid disease, but in this series of autopsied cases, it was not used.

One of the simplest and most valuable x-ray findings was the globular configuration of the cardiac silhouette in the anteroposterior position. Frequently, the shadow is triangular and suggestive of pericarditis with effusion except that there is no widening of the shadow of the base of the heart.

The pulmonary fields were clear in 15.55 per cent of our patients, many of whom had mitral disease with severe heart failure. This explains the relative insignificance of the dyspnea, the low frequency of decubitus dyspnea, and the absence of paroxysmal dyspnea in these patients with advanced cardiac insufficiency.

SUMMARY AND CONCLUSIONS

An analysis has been made of the signs and symptoms in fifty patients with severe tricuspid lesions confirmed by autopsy. These fifty patients comprised 33.33 per cent of all rheumatic cases that were found in 250 autopsy reports at the National Institute of Cardiology (Mexico).

A correct clinical diagnosis was made in 34 per cent of the tricuspid cases.

The most important facts found in this study were the following:

1. In all cases with rheumatic etiology, the tricuspid lesion co-existed with a mitral lesion; in many cases an aortic lesion was also present. Only exceptionally were all four valves involved.

2. A systolic murmur, heard over the xiphoid, constituted the basis of the diagnosis of tricuspid disease in all patients in whom the lesion was recognized in life.

3. In eight patients the fact that a tricuspid as well as a mitral murmur was present was determined by the fact that the acoustic characteristics were distinct in the mitral and tricuspid areas. This was appeciated without employing special technique.

4. In ten patients the modifications of the xiphoid systolic murmur produced by deep inspiration and by postinspiratory and postexpiratory apnea (method of Rivero Carvallo[25]) were studied. In 90 per cent of the patients thus studied, the murmur increased in intensity during postinspiratory apnea; in several cases also the murmur became higher pitched during the held inspiration. A deep, held inspiration generally had the opposite effect upon a mitral systolic murmur. This fact was of great help in recognizing the tricuspid origin of the murmur.

5. A number of clinical manifestations which together or singly aid in the recognition of tricuspid involvement are discussed.

6. The only constant finding in our series was hepatomegaly of varying degree and character. In 90 per cent of the patients the consistency of the enlarged liver was increased.

7. The other signs, although at times more specific, are found less often. The striking infrequence of dyspnea of decubitus and of paroxysmal dyspnea, despite the presence of severe cardiac insufficiency, is undoubtedly related to the fact that the lung fields did not show x-ray evidence of congestion in 15.55 per cent and that no cough was present in 30 per cent of the patients with tricuspid disease. The color resulting from the combination of cyanosis, pallor, and subclinical jaundice, as described by Shattuck, was observed in only 8 per cent of our patients. We observed cyanosis alone in 56 per cent, distention of the jugular vein in 86 per cent, systolic jugular pulse in 36 per cent, and hepatic pulsation in 42 per cent. Among those patients subjected to liver function tests, 75 per cent showed functional deficiency.

8. Two electrocardiographic signs were found to be suggestive of a tricuspid lesion: the first consists in a deviation of $\hat{A}_P$ to the right of more than 60 degrees (51.6 per cent) and the second, in a delay of 0.04 second or more in the onset of the intrinsic deflection in V_1 and V_2 (63.62 per cent).

9. The most important x-ray signs in the order of their clinical value and frequency were marked hypertrophy of the right auricle (48.88 per cent) or right ventricle (44.44 per cent); dynamic pulsations of the aortic type in the absence of an aortic lesion (4 per cent); double contour in the region of the right auricular salient, not produced by interposition of the right bronchus (17.77 per cent); dilatation of superior vena cava (17.77 per cent); triangular or globular appearance of the cardiac silhouette in the anteroposterior view.

10. It is concluded that the diagnosis of a tricuspid lesion, so infrequently made in the patient, can be made successfully by ordinary clinical methods in the majority of the cases.

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Clinical Reports

CONGENITAL PULMONARY STENOSIS WITH CLOSED INTERVENTRICULAR SEPTUM

Report of a Case Associated With Patent Foramen Ovale and Slight Tricuspid Stenosis

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IN MAUDE ABBOTT'S classic *Atlas of Congenital Cardiac Disease*[1] there are described nine cases of pulmonary stenosis in which all septa were closed and sixteen cases of pulmonary stenosis in which only the foramen ovale was patent. These two groups constitute the rarer forms of pulmonary stenosis as compared to the more numerous group in which the interventricular septum is defective. In 1942, Rossman[2] described an additional case of pulmonary stenosis with closed interventricular septum and patent foramen ovale in a 4-month-old child. He listed this as the eighteenth of its type, including Abbott's original sixteen. It is not clear whether this report includes a case reported by Blackford and Parker[3] in which the foramen ovale was anatomically open, although considered to be functionally closed. To these may be added the case of Garrison and Feldt[4] (all septa closed) and two cases (Cases 5 and 9) from a recent series by Currens, Kinney, and White,[5] one with all septa closed and one with patency of the foramen ovale.

To that group of congenital pulmonary stenosis with closed interventricular septum but patent foramen ovale we wish to add the case which will be described.

CASE REPORT

H. K., a 15-year-old white boy, was first admitted to the University Hospital on Sept. 10, 1940. He complained of painful swelling of the glands of the left axilla, and of fever, headache, and general malaise of about two weeks' duration. Physical examination relative to these complaints revealed pharyngitis and generalized lymphadenopathy, one node in the left axilla being especially enlarged. The leucocyte count was 11,000 but nothing unusual was noted in the blood smear. Blood agglutination tests were negative, but a heterophil antibody reaction was not performed.

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Examination directed attention to the cardiovascular system, and questioning brought out these points of importance. He had been "sickly" all of his life and had always suffered from shortness of breath. Climbing a single flight of stairs induced dyspnea. He had never been able to participate in the usual exercises or games of his companions. For several years he had had unexplained nose bleeds. There was no history of his having been a "blue baby," nor of cyanosis since birth. No history of rheumatic involvement was obtained. On examination he was somewhat malnourished. There was no cyanosis or clubbing of the fingers. The thorax was of the "pigeon-breast" type with an increased anteroposterior diameter. The lungs were clear. The blood pressure was 100/65. The heart was considered to be slightly enlarged, the left border of dullness being one centimeter beyond the midclavicular line. There was a loud systolic murmur over the entire precordium, with its point of maximum intensity over the second intercostal space to the left of the sternum. This murmur was well transmitted up the neck vessels on the left side and toward the left axilla. It was described as being "swishing or rasping" in quality. No mention was made of the intensity of the pulmonic second sound. Examination was otherwise essentially negative. An x-ray film of the chest (Fig. 1) showed fullness in the region of the

Fig. 1.—Teleroentgenogram showing the prominent pulmonary conus, hypertrophied right auricle, and the blunt apex indicative of right ventricular hypertrophy. Note the shadow of the great veins to the right of the sternum.

pulmonary artery and right auricle. The electrocardiogram (Fig. 2) showed intraventricular block with right axis deviation. The diagnosis made by the house staff at this time was possible patency of the ductus arteriosus and interventricular septum. The patient was discharged Oct. 13, 1940.

He was readmitted eighteen months later. In the interim he had experienced occasional attacks of dyspnea but had felt well until two weeks before admission when he developed frequency of urination, with reddish discoloration of the urine. At the same time his feet began to swell. Soon after, he noted swelling of the face and hands and he complained of persistent headache. Examination revealed moderate generalized edema. The blood pressure was 150/100. The heart findings were the same as those observed on the first hospital admission except that a systolic thrill, in addition to the murmur previously described, was noted. There was no ascites. There was Grade 3 edema of the ankles. Urine examination showed cellular elements and albumin, consistent with a diagnosis of acute glomerular nephritis. On this admission, a diagnosis of pulmonic stenosis with interventricular septal defect was made on the basis of the cardiac findings. The patient responded promptly to the routine treatment for nephritis and was discharged on April 26, 1941.

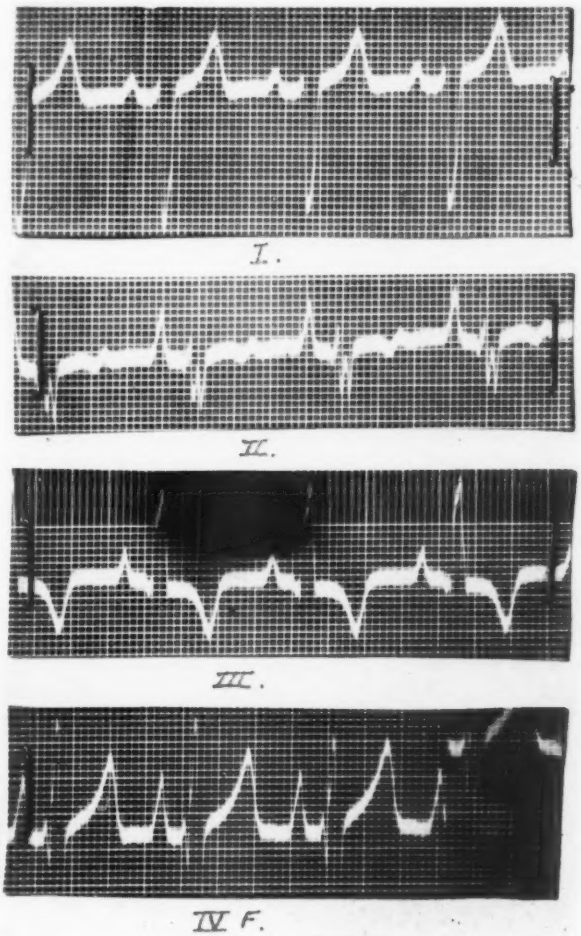

Fig. 2.—Electrocardiogram showing right ventricular preponderance, abnormally high P waves, and intraventricular block.

He was next admitted on Feb. 28, 1942, complaining of hemoptysis. Three weeks prior to admission he had developed a cold and cough and had begun to bring up small amounts of bright red blood. No cyanosis was noted. Pharyngitis and rhinitis were present. The heart was thought to be slightly enlarged. Auscultatory findings were as before. There was a mild degree of polycythemia, the red cell count being 6.2 million and the hemoglobin about 17 grams. For the first time a diagnosis of interauricular septal defect was made.

About one year later he was admitted again for acute pharyngitis. By this time cyanosis and clubbing of the fingers had appeared; the cyanosis was of moderate degree and the clubbing was minimal. Two distinct murmurs were now audible. One was maximal over the pulmonic area and was well transmitted along the left clavicle. The other was best heard over the third and fourth intercostal spaces to the left of the sternum. X-ray examination showed dilatation of the pulmonary artery, what was thought to be widening of the aorta to the right of the sternum, and enlargement of the right auricle. The electrocardiogram still showed intraventricular block and right axis deviation. The circulation time from arm to tongue was 14.5 seconds. Blood cultures and a blood Wassermann test were negative. A teleroentgenogram showed the following measurements: Midline to left border, 9.5 cm.; midline to right border, 4 cm.; total cardiac diameter, 13.5 cm.; and internal intrathoracic diameter, 24 centimeters. Mild polycythemia was still present. The diagnosis at this time was tetralogy of Fallot.

The next admission was on Jan. 19, 1944, for another attack of acute pharyngitis. Hemolytic streptococci were cultured from the nasopharynx. On this admission a diagnosis of tetralogy of Eisenmenger was made and this was maintained until the death of the patient. It was thought that all four cardinal points were clinically proved. The dilated pulmonary artery was visualized repeatedly both in films and under the screen. The interventricular septal defect was thought to be confirmed by the presence of intraventricular block in the electrocardiogram. Right ventricular hypertrophy was demonstrated by right axis deviation in the electrocardiogram and by the typical appearance of the x-ray shadow. Dextroposition of the aorta was thought to be seen in x-ray films and on the fluoroscopic screen. Cyanosis, clubbing, and polycythemia confirmed the impression of a venous-arterial shunt. Many clinics were held on this patient as a typical case of the Eisenmenger complex.

Three brief admissions late in 1944 are pertinent only in that it was evident that his cardiac reserve was becoming progressively less. Cyanosis was more marked. He was still able to work as a taxi driver. The final admission was on Nov. 11, 1945, when the diagnosis was acute upper respiratory infection and possible atypical pneumonia. He showed no evidence of heart failure on admission. The leucocyte count was 9,750 and the hemoglobin was 21 grams. On the following day there were moist râles throughout both lungs and a gallop rhythm was audible. Supportive treatment was without effect. Cyanosis increased and he died on Nov. 12, 1945, at the age of 20 years.

Necropsy.—The examination was performed about four hours after death. The unopened pericardial sac was much enlarged especially to the right and toward the base so that the outline was more globular than usual. There was a slight excess of clear serous fluid enclosed.

The heart weighed 520 grams. The transverse diameter across the ventricles was 13 centimeters. Inspection and palpation of the organ, in situ, disclosed pronounced preponderance of the right chambers, particularly of the ventricle. The right auricle was dilated and hypertrophied, far exceeding the left in volume and in thickness of muscle. The foramen ovale (Fig. 3) was freely patent from right to left in a slightly oblique direction, the defect measuring 1 x 0.6 centimeters. The tricuspid ring measured 10 centimeters. The valve was grossly deformed so that only two cusps (anterior and medial) were clearly identifiable. These were thickened and contracted and the chordae tendineae were correspondingly thickened and shortened; the anterior leaflet was somewhat more affected. On the line of closure were a number of small, discrete, firmly attached, moist fibrous nodules, the largest measuring about 0.3 cm. in its greatest diameter (Fig. 3). The right ventricle was of increased capacity. The muscle was greatly thickened, varying from 1.2 to 1.8 cm. in diameter. The bundles were coarsely hypertrophied and there were numerous minute fibrous scars. The conus appeared slightly narrowed but the lumen was not constricted.

The pulmonary valve was exposed from above and presented a remarkable picture of stenosis (Fig. 4). It was composed of three distinct cusps of equal size, but all were thickened and

Fig. 3.—View of the right chambers showing myocardial hypertrophy and tricuspid valvular disease. The arrow indicates the foramen ovale.

Fig. 4.—The pulmonary valve as seen from above with the artery opened and retracted. The degree of stenosis, although actually extreme, is slightly exaggerated in the fixed specimen.

fused together along the free edges so as to constitute a nearly complete diaphragm. In the center of this fused valve was a smooth rounded aperture, about 0.2 cm. in diameter when under slight tension. Water contained in the conus seeped through the valve very slowly. The ring measured 5.8 centimeters. The pulmonary artery was of about the same circumference and was essentially normal in structure and distribution of branches. The ductus arteriosus was closed.

The left chambers and valves were contrastingly normal on gross examination. There was slight dilation of the left auricle. The ventricular myocardium measured 1.2 cm. in thickness. The interventricular septum was intact. The mitral valve was well formed, of delicate structure, and fully competent. The aortic ring measured 6 centimeters. The valve cusps were thin and pliable. The sinuses and the coronary arteries were normal. There was very slight atheromatosis of the systemic aorta.

Microscopic study of the myocardium confirmed the hypertrophy and scarring of the right ventricular muscle. The fibrous scars were of very small size and of indiscriminate distribution. They appeared to be secondary to degeneration and atrophy of scattered muscle fibers since these changes were existent. There was some condensation and clustering of sarcolemma cells in such foci, and occasionally there were a few infiltrating round cells. There was no suggestion of rheumatic disease. The intimate vasculature was congested and there were scattered foci of recent interstitial hemorrhage. Slight interstitial edema was present. There was considerable loose fibrous thickening of the mural endocardium in one section.

A section of the tricuspid valve showed irregular fibrosis having a myxomatous character in some areas. An included marginal nodule was made up of similar myxomatous fibrous tissue. There were occasional round cells beneath the covering endocardium and around the dilated capillaries present in the valve leaflet proper.

The immediate cause of death was confluent lobular pneumonia. The left lower lobe was more affected and showed some areas of frank suppuration. Cultures were not obtained but masses of cocci were present in microscopic sections of the pulmonary lesions and in the overlying pleural exudate. The remainder of the examination revealed no important findings. There was evidence of chronic passive congestion of the abdominal viscera. The kidneys showed small healed infarcts. There was no evidence of pulmonary tuberculosis which has been described as being a frequent complication of pulmonary stenosis.[5]

COMMENT

In retrospect, the clinical diagnostic error was brought about by logical but false deductions on evidence pointing especially to two components of the Eisenmenger complex. Perhaps the most misleading feature was the assumption of interventricular septal defect on the basis of electrocardiographic evidence of intraventricular block. Blackford and Parker[3] observed the same phenomenon in a strikingly similar case and were led into the same clinical error. We agree with them that the block was really produced by myocardial (conduction system) damage and that the probable cause was ischemia. A second confusing feature was the radiographic evidence of pulmonary artery dilatation; it now appears that this dilatation well might have been the so-called "dynamic dilatation," actually existent during life but, of course, not evident after death. It also appears that the radiographic fallacy of the dextroposed aorta was probably a shadow of the great veins. The correct clinical diagnosis might have been reached by the use of right heart catheterization to demonstrate abnormally high oxygen content of the auricular blood, or the employment of a contrast medium to accurately locate the septal defect. From the practical therapeutic standpoint, however, the diagnostic error was unimportant and for this reason these procedures may not have been entirely justifiable.

SUMMARY

An additional case of congenital pulmonary stenosis without ventricular septal defect is described. Functional patency of the foramen ovale and tricuspid valvular disease with minor stenosis were associated anomalies. The patient lived to be 20 years of age and developed overt circulatory deficiency only during the last two and one-half years of his life. Clinical diagnostic difficulty resulted from evidence of intraventricular block simulating septal defect.

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FAMILIAL CONGENITAL COMPLETE A-V HEART BLOCK

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ALTHOUGH, over the past few decades many cases of congenital complete A-V heart block have been reported in the literature, Aylward was the first to suggest that there may be a familial predisposition to the development of such a conduction defect.[1] The basis for his opinion was his observation that a slow pulse rate (below 50 per minute) was present in each of two siblings shortly after their birth. At the time, however, corroborative electrocardiograms were not included. Subsequently, Aitken[2] stated that she had obtained electrocardiograms of both of Aylward's patients and had confirmed the existence of complete heart block. Unfortunately, reproductions of the records were not published. It is the purpose of this report, therefore, to demonstrate with the support of graphic evidence the occurrence of complete congenital A-V heart block in two siblings, one parent of whom suffered from the effects of a different type of anomalous conduction (Wolff-Parkinson-White syndrome).

CASE REPORT

The 33-year-old father of the two children, whose case histories are to be reported in detail, first came to the attention of one of us (M. H. W.) early in 1943. At that time he was troubled with attacks of paroxysmal tachycardia from which he had been suffering for the past fifteen years. An electrocardiogram was obtained during one of his attacks, and the diagnosis of a supraventricular form of paroxysmal tachycardia was confirmed (Fig. 1). Records made after subsidence of the attack showed that he was suffering also from an anomaly of conduction characterized by a short P-R interval and a bizarre QRS complex (Fig. 1). Electrocardiograms of his wife and his dizygotic twin brother were entirely normal (Fig. 2).

Several weeks later his first child, then five years of age, was brought to one of us (M. H. W.) for an examination because of the fact that he had been known to have a slow heart rate (less than 60 per minute) since the age of two. This bradycardia was first discovered by the attending physician when the child was being treated for a simple respiratory infection. As far as the parent was aware, the child had suffered no ill effects as the result of this slow heart rate and had always been able to play and exercise without disability or cyanosis. He had had none of the usual cardiotoxic diseases, such as diphtheria, scarlet fever, or rheumatic fever. His mother had not been ill during his fetal life, and birth was spontaneous and uncomplicated. The electrocardiogram, which was made when he was five years of age, showed the presence of complete A-V heart block, with a ventricular rate of 60 per minute (Fig. 3). The physical examination revealed no significant changes other than the bradycardia, which was not materially modified by exercise. X-ray studies of the heart and lungs demonstrated no abnormalities. A brother,

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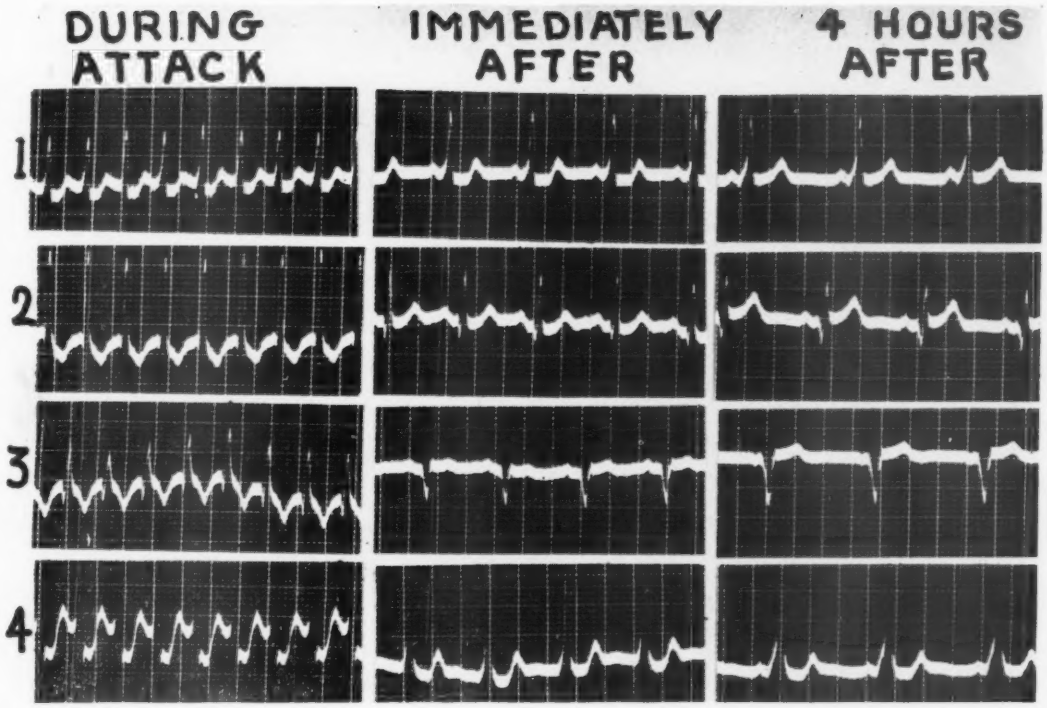

Fig. 1.—Electrocardiograms of the male parent during and after an attack of paroxysmal tachycardia. Note the shortened P-R interval and bizarre QRS complex characteristic of the Wolff-Parkinson-White syndrome during the period of normal sinus rhythm.

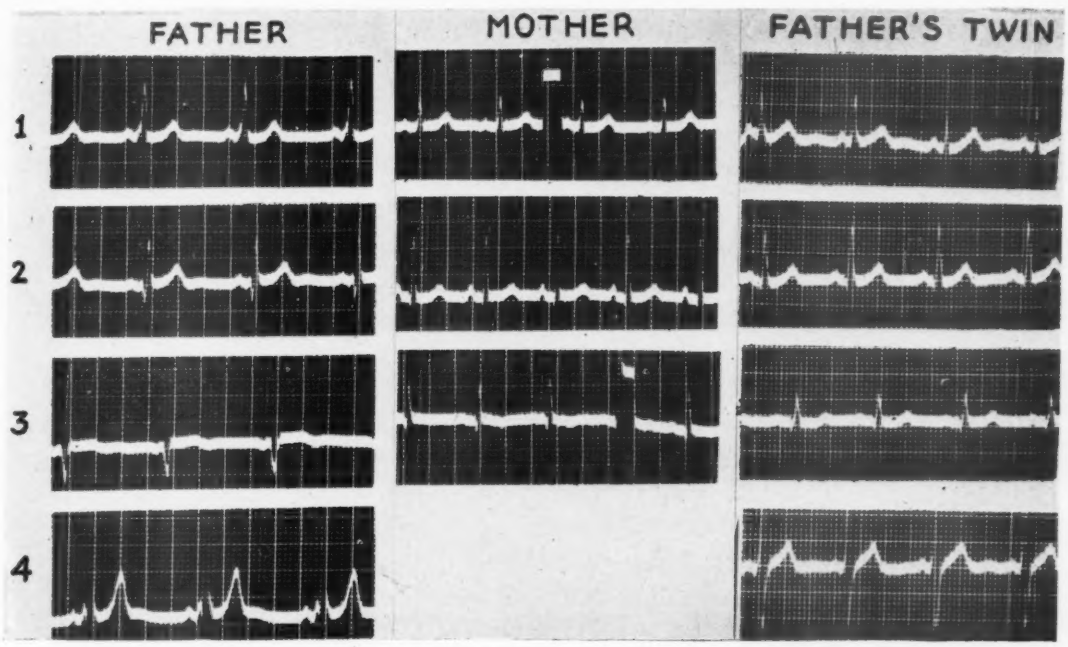

Fig. 2.—Compare the normal P-R intervals and normal QRS complexes in the female parent and the male parent's dizygotic twin with the shortened P-R interval and bizarre QRS complex of the male parent.

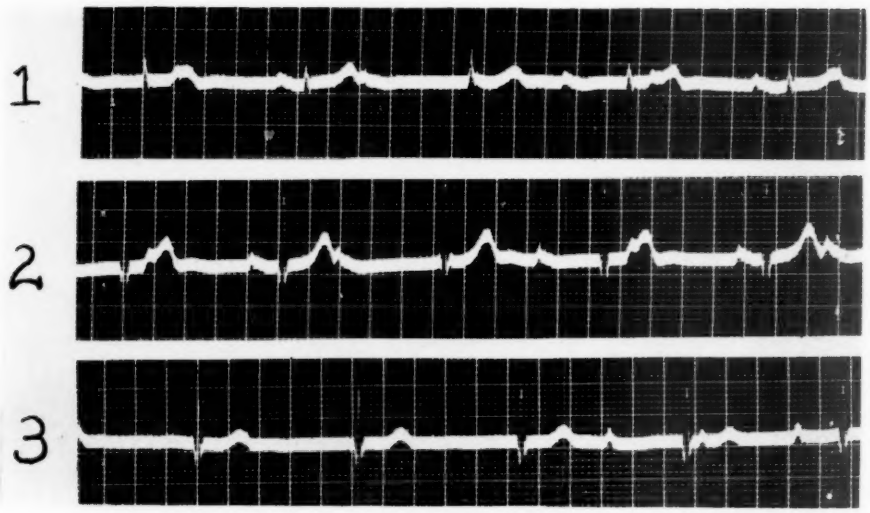

Fig. 3.—Electrocardiogram of the surviving sibling, showing the presence of complete A-V heart block with a ventricular rate of 60 per minute.

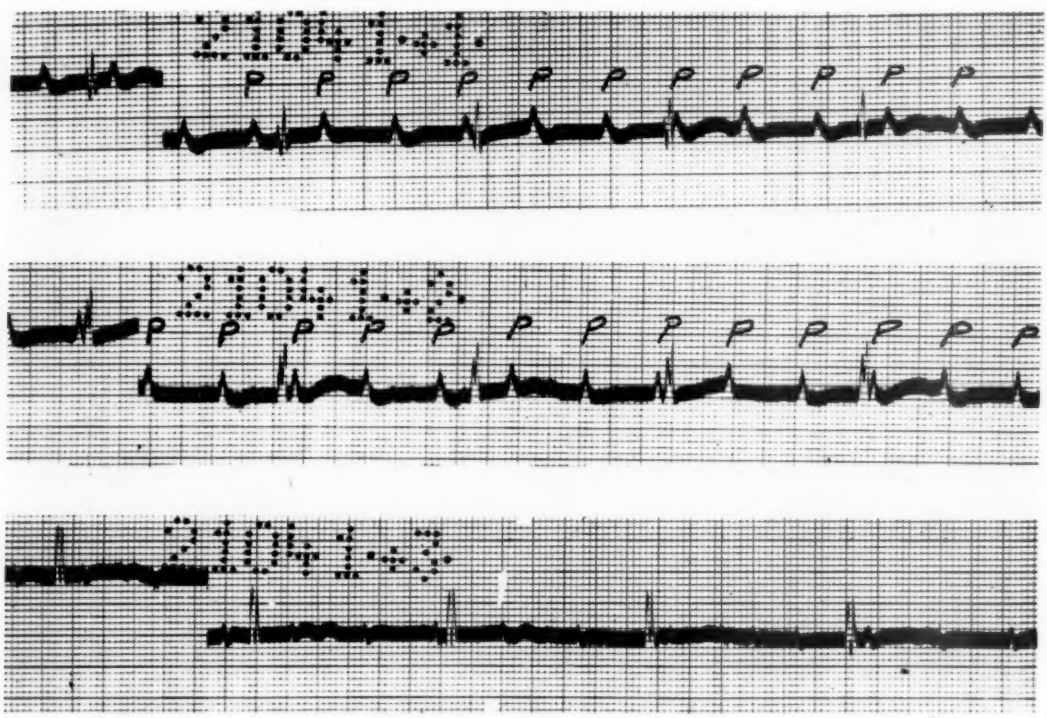

Fig. 4.—Electrocardiogram of the nonsurviving sibling showing the presence of complete A-V heart block, the ventricular rate being 50 per minute.

two years younger, has never shown evidence of a cardiac lesion and has remained in excellent health since his birth.

During the mother's third and last pregnancy, at which time she was 29 years of age, it was noted that the fetal heart rate was unusually slow and averaged approximately 50 beats per minute. An attempt to make an electrocardiogram of the fetus was unsuccessful. Delivery occurred at term and was uncomplicated. Immediately after birth the child showed no evidence of cardiac embarrassment but approximately thirty-six hours afterward, he became increasingly cyanotic and showed progressive respiratory difficulty. A loud systolic murmur became audible over the heart. The rate remained around 50. The child lived three days and died during an attack of respiratory distress. An electrocardiogram had been made about thirty hours before death and showed evidence of complete A-V heart block, with a ventricular rate of 50 per minute (Fig. 4).

The results of autopsy* findings are as follows: "The heart was slightly large, but its general configuration was normal. The ductus arteriosus which was widely patent was only slightly smaller in caliber than the pulmonary artery. There was a constriction in the distal portion of the aortic arch just proximal to the entrance of the patent ductus arteriosus" (Fig. 5). "The interior of the heart was normal, and the interventricular septum was intact. The heart and aorta weighed 40 Gm., and all the coronary vessels and the myocardium were normal. The section of muscle

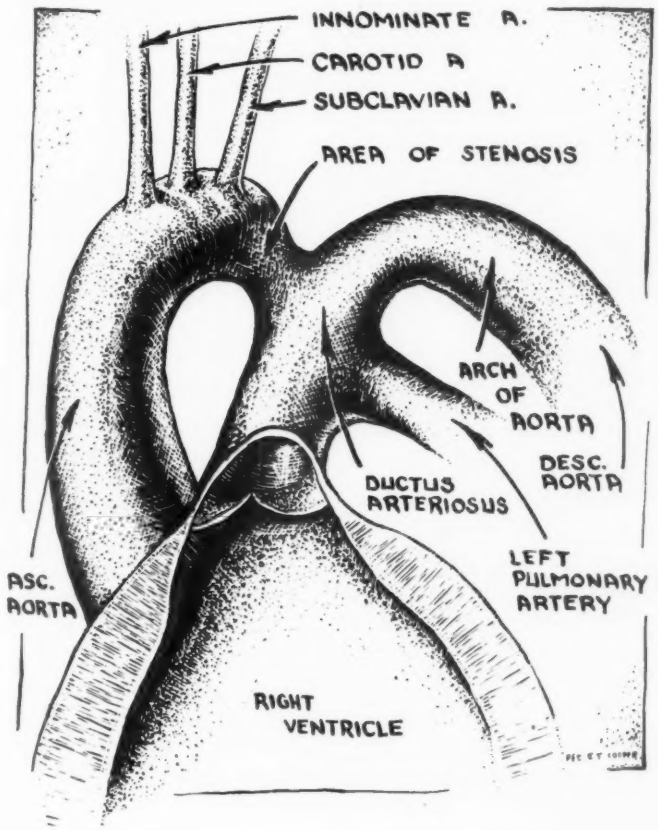

Fig. 5.—Schematic drawing of the anomalous vessels in the case of the nonsurviving sibling with congenital complete A-V heart block.

*Autopsy was performed by Dr. Edith L. Potter, at the University of Chicago Lying-In Hospital.

from this child's heart failed to show anything which could be identified as a bundle of His. However, the significance of this finding is questionable since at times it is impossible to identify this structure in normal hearts."

DISCUSSION

The diagnosis of congenital complete A-V heart block in the two siblings described in this report seems to be unquestionable, according to the criteria established by Yater.[3] It should be pointed out, however, that in both instances there was no evidence of an associated interventricular septal defect, even though statistical studies indicate a high incidence of this anomaly in children with congenital heart block.[4] It is also of interest that the male parent suffered from another type of anomalous conduction (Wolff-Parkinson-White syndrome), but in the absence of additional evidence it would be hazardous to suggest that any causal relationship exists between the two.

SUMMARY

1. Evidence is presented to indicate that familial congenital complete A-V heart block is a clinical entity.

2. The presence of an anomaly in conduction in one of the parents (Wolff-Parkinson-White syndrome) is briefly discussed.

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Abstracts and Reviews

Selected Abstracts

Jaffe, Rudolf: Chronic Isolated Myocarditis. Cardiologia **10:** 402, 1946.

In 5,000 autopsies in Venezuela, 500 cases of isolated myocarditis were found. Identifiable underlying heart disease was absent in all but two patients who showed Aschoff bodies. Clinically, heart failure and noncharacteristic electrocardiographic changes were present. The disease lasted months or years. Some patients died suddenly. On autopsy the hearts were enormously dilated, without hypertrophy (weight rarely over 400 grams), and flabby. The myocardium was cloudy, friable, and at times showed small scars. Mural thrombi were often present. Histologically, the myocardium showed infiltration with round cells, plasma cells, and eosinophiles. Focal or diffuse fibroblastic or granulomatous proliferations progressing to scars were found alone or in combination with cellular infiltration. This picture is identical with Fiedler's or the isolated myocarditis of the Americans.

Myocardial fibrosis is considered the end picture of diffuse inflammation. The author suggests a classification into specific (bacterial, rheumatic) and nonspecific myocarditis. In his series he found a striking coincidence with three other diseases: syphilis was present in 44 per cent, bilharziasis in 48 per cent, and necatoriasis in 28 per cent. The percentage incidence of these three diseases was much higher than in the patients of his series who did not have myocarditis. Some patients had other infectious diseases or beriberi.

All cases showed the same anatomicohistological picture. Further routine histologic examinations showed as early stages of the diseases focal fatty degeneration which is considered the visible expression of cellular damage. The later changes are a reaction to irritation or are a regenerative process. Thus, only the muscle damage is a direct consequence of the underlying disease; all other changes are secondary. The nature of the muscle damage is thought to be allergic, with nutritional factors superimposed. All the mentioned diseases produce muscle damage with antibody formation. In a subsequent injury, an allergic reaction occurs, producing the picture of myocarditis. Two different diseases may cause it; one may sensitize, the other may produce the allergic reaction. LENEL.

Proger, S., and Dekamas, D.: Some Effects of Injected Cytochrome C in Myocardial and Cerebral Anoxemia in Man. J. of Pediat. **29:**729 (Dec.), 1946.

Cytochrome C exists in organs in suboptimal amounts. Therefore, as there seems to be relatively more cytochrome oxidase present than is required for activation by the small amounts of cytochrome C present, it is reasonable to suppose that an added supply of cytochrome might be effective in combatting anoxemia. Material for testing this hypothesis was obtained by the Keilin and Hartree method of preparing cytochrome C. This material seems to be both nontoxic and stable. Four patients who showed marked electrocardiographic response following ten to twenty minutes exposure to an atmosphere containing 10 per cent oxygen and 90 per cent nitrogen were selected for this experiment. It was found that 60 mg. of cytochrome C given intravenously prevented these changes. The cerebral effects of anoxia, as measured by visual discrimination and code transliteration tests, could also be prevented by the same dose of cytochrome C.

The effects of cytochrome C were also tried clinically on four patients with angina pectoris, and found to be moderately effective in increasing the capacity for physical exertion. The effects of the continued daily administration of cytochrome C on Raynaud's disease and on patients with intermittent claudication were more striking and the benefits more marked. In acute myocardial infarction, no improvement was observed.

These experiments are of great interest and the results may be applicable to a great variety of conditions in which anoxia is of prime consideration. HAUB.

Muntz, H. H., Ritchie, J. O., and Gatch, W. D.: Adrenalin Producing Tumor (Pheochromocytoma) Containing 2,300 Milligrams of Adrenalin. Ann. Int. Med. **26**:133 (Jan.), 1947.

A case of pheochromocytoma in both adrenal glands confirmed by necropsy is described. The patient, a 39-year-old woman, died while being operated on for removal of a right-sided adrenal tumor; the existence of which had been suspected during life because of spontaneous and induced crises of marked hypertension, along with x-ray visualization of a defect of the superior calyx of the pelvis of the right kidney, which was presumably due to a mass overlying the superior pole of the kidney. Induction of hypertensive crises during life had followed the intravenous administration of histamine acid phosphate or massage of the palpable tumor mass.

The significant findings at autopsy consisted of a well-encapsulated tumor of the right adrenal gland, about the size of an orange and weighing 350 grams; two spherical nodules in the medulla of the left adrenal gland, each measuring about 1 cm. in diameter; and a tumor of the thyroid gland with metastasis to the regional lymph nodes. Histologic examination of the bilateral adrenal tumors demonstrated in them the typical architecture of pheochromocytoma, whereas the cellular pattern of the tumor in the region of the thyroid gland and its regional lymph nodes was characteristically carcinomatous. By means of biologic assays of the single large pheochromocytoma, it was calculated that it contained 671 mg. of epinephrine for each 100 grams of tumor. This is equivalent to a total content of 2.35 grams of epinephrine, an amount estimated to be present, in physiologic proportions, in the adrenal glands of 31 cattle or 261 normal men. WENDKOS.

Rosenbaum, F. F.: Right Ventricular and Right Auricular Hypertrophy of Obscure Origin. Ann. Int. Med. **26**:76 (Jan.), 1947.

Two instances of idiopathic right ventricular hypertrophy and dilatation in adult women are described. Autopsy examination revealed, in one case, associated dilatation of the entire pulmonary arterial tree without disease of the pulmonary arterial walls, and in the other, dilatation of the right auricle and moderate hypertrophy of the left ventricle without any other significant finding. Recognizable congenital anomalies were not present. In both cases, the usual causes of cor pulmonale were excluded. The clinical features of the syndrome are also summarized. The constant occurrence of cyanosis and ascites in the disorder is noted. The electrocardiographic characteristics are also discussed, with attention directed specifically to the occurrence of right axis deviation and large, slightly delayed R waves in precordial leads derived from the right hemothorax. Reports of similar cases in the literature are thoroughly reviewed by the author. He accepts only six as being authentic and six others as probably authentic examples of the same syndrome. WENDKOS.

Solomon, S., and Irwin, C. W.: Cutaneous Diphtheria with Toxic Myocarditis: Report of a Total Case With Necropsy Finding. Ann. Int. Med. **26**:116 (Jan.), 1947.

A case of cutaneous diphtheria complicated by acute myocarditis is described. The sudden development of complete A-V heart block established the diagnosis of cardiac involvement during life. Microscopic sections of the ventricular myocardium, at autopsy, revealed scattered foci in which the myocardial fibers had disappeared leaving only stroma and a small infiltrate of lymphocytes, plasma cells, and macrophages. Bacteriologic study of the skin lesions had demon-

strated the presence of Klebs-Löffler bacilli, virulent to nonprotected guinea pigs, in pure culture. Because of their experience with this case, the authors emphasize the need for early and adequate treatment with diphtheria antitoxin whenever cutaneous diphtheria is suspected.

WENDKOS.

Bushong, B. B.: Traumatic Rupture of the Aortic Valve: Report of Two Cases, One a Proved and the Other a Probable Example of This Condition. Ann. Int. Med. **26**:125 (Jan.), 1947.

Two cases of musical diastolic murmurs, presumably due to traumatic rupture of the aortic valve, are reported. One was a 50-year-old man who had apparently been in good health until he developed chest pain and dyspnea while attempting to extricate himself from a truckload of fence posts which had knocked him down. Sixty-nine days after this injury, he died of progressive cardiac failure. The autopsy revealed a transverse tear along the right anterior and posterior aortic valve leaflets which allowed the cusp margins to prolapse into the ventricle. Although no associated disease of the aortic valve or aorta was described, the weight of the heart was increased to 600 grams and hypertrophy and dilatation of both ventricles and auricles were present.

The other case was that of an 11-year-old boy who was not suffering from symptoms of cardiac failure but was examined because of the sudden development of a buzzing sound in the chest which presumably followed a blow to the chest during a boxing lesson. No other murmurs were audible. Peripheral signs of aortic incompetency were well pronounced. No history of rheumatic fever could be obtained. The electrocardiogram was normal. A sound tracing showed the typical pattern of the "cooing-dove" murmur.

WENDKOS.

Robbins, L. L.: The Technique of the Roentgenologic Demonstration of Pulmonary Infarct. Am. J. Roentgenol. **56**:736, 1946.

The importance of early diagnosis of pulmonary infarct has become more evident with the institution of modern therapeutic methods for preventing and combating the sequelae of infarction.

Approximately 75 per cent of infarcts occur in the lower portion of the lung. The size of the infarct may vary from a small linear lesion lying against the pleura to a large lesion occupying the greater portion of a lobe. The shape of the infarct is dependent on its location, but it is always peripheral with its long axis parallel to the pleura. The shadow as a rule has a curved proximal margin. The infarct is at first indistinct but gradually becomes more sharply defined. In a period varying from days to a month it assumes a linear shape and may finally disappear except for a very fine linear scar.

At least two views, a posterior-anterior and a lateral view of the chest, is the minimal number of films necessary to demonstrate adequately an infarct. If the condition of the patient permits, roentgenoscopy of the chest is very helpful. Adequate evaluation of the thoracic dynamics and optimum position for making films is possible following roentgenoscopy. Spot films during fluoroscopy frequently will better demonstrate infarcts than a full 14x17 film.

The author has found that the Merrill modification of the Fuch's technique, using a high optimum kilovoltage and varying the milliampere seconds with the size of the patient, has resulted in a film of more uniform quality. A roentgen differential diagnosis is included in the paper.

ZION.

Lindgren, E.: The Roentgen Diagnosis of Arteriovenous Aneurysm of the Lung. Acta radiol. **27**:585 (No. VI), 1946.

The author stresses the distinction, first made by Reid in 1925, between congenital arteriovenous aneurysm and acquired arteriovenous fistula. The congenital lesions have not been found to enlarge the heart, regardless of their proximity to it. Three cases of arteriovenous aneurysm of the pulmonic vessels are reported in addition to the two in the literature.

The salient clinical characteristics were a systolic bruit over the aneurysm, heard through the chest wall; clubbed fingers; cyanosis of varying severity; normal heart size; and a characteristic roentgen picture of a nonpulsatile density, with vascular markings communicating with

it, in the lung field. The density becomes larger during the Valsalva and smaller during the Müller experiments. Body section films and angiocardiography were helpful in the differential diagnosis. The most common clinical complications, in addition to poor exercise tolerance, were hemoptysis and syncopal or focal cerebral manifestations of transitory nature attributed to air embolism.

Case 1, a 30-year-old man, had an arteriovenous aneurysm in the left chest, and a presumably unrelated mitral stenosis. By oxygen saturation studies, the author estimated that 28 per cent of the pulmonary blood was short-circuited through the communication. Case 2, a 29-year-old man, had hereditary hemorrhagic telangiectasis with multiple lung arteriovenous aneurysms and many blue-black dots scattered over his skin representing smaller lesions. The two largest pulmonary aneurysms were close together in the right lung field, over which a systolic bruit could be heard. The heart was normal. Case 3, a 25-year-old man, had a left lower lobe aneurysm which caused frequent small hemoptyses. He had been thought to have congenital heart disease or pulmonary tuberculosis during his twelve years of symptoms. The arterial oxygen saturation was 83.8 vols. per cent after fifteen minutes of 100 per cent oxygen. There were no evidences of a cardiac lesion.

The two largest aneurysms in Case 2 and the left lower lobe lesion in Case 3 were successfully resected by Crafoord. A continuous thrill and definite systolic pulsation could be felt in the exposed aneurysms. Cyanosis disappeared after the operation and the immediate convalescence was satisfactory in both cases. Heart volume of both patients increased slightly following the resections. SAYEN.

Broch, O.: The Electrocardiogram in Derangements of the Organism's Water and Electrolyte Metabolism. Acta Med. Scandinav. **126**:157 (Nos. II-III), 1946.

The literature relative to electrocardiographic change associated with calcium, potassium, and acid-base imbalance is reviewed, as well as that on dehydration, acute hemorrhage, and traumatic and anaphylactic shock. The author emphasizes that the RS-T segment changes associated with fluid and electrolyte disturbances are well known, but since the two generally occur together, it is not established whether lowered coronary blood flow or the effect locally on the heart muscle of change in metabolites is responsible for these changes.

Electrocardiograms of 13 cases of severe dehydration were taken before and during treatment. The series included cases of acidosis, alkalosis, gastroenteritic diarrhea, shock, asphyxia, and pyloric or lower small intestinal obstruction. They had in common an electrocardiographic picture of RS-T segment depression (one to four mm.) usually greater in Leads II, III, and CF_4 than in Lead I. The height and sharpness of the T waves were sometimes increased. The RS-T segment depressions vanished in every case immediately after the administration of one or two liters of normal saline intravenously and did not return, although the chemical imbalances had not yet been corrected. The T waves often remained low for a few days to three weeks thereafter and there was sometimes a prolongation of the Q-T interval. Routine chemical studies included total base, CO_2 and hemoglobin determinations, and usually serum chlorides. The author believes the electrocardiographic changes were due to diminished blood volume with secondary reduction of coronary arterial flow and not to disturbances in chemical equilibrium.

An additional part of the study was the administration of potassium salts to four uremic patients with elevated serum potassium levels. All developed further increase in serum potassium and the T-wave height increased in their electrocardiograms (inverted T waves becoming less inverted). The Q-T interval did not change. SAYEN.

Biorck, G.: Five Cases With Pre-Excitation Electrocardiograms. Acta Med. Scandinav. **125**:465 (No. V), 1946.

Of five cases of pre-excitation, two showed a short P-R interval, slurred upstroke of QRS complex, and attacks of paroxysmal tachycardia typical of the Wolff-Parkinson-White syndrome. Change of position and a sympathomimetic drug influenced the pattern considerably in one of these cases. The other three cases had P-R intervals of 0.12 second or more, but a deformity of the upstroke of QRS in various leads and an abnormal RS-T segment and T-wave pattern, which

in two cases involved only Leads II and III. The tracing changed at times to the abnormal pattern during exercise or amyl nitrite inhalation, but at other times the abnormal pattern appeared and disappeared spontaneously. One case showed two abnormal patterns. The author's Figs. 4*C* and 3*B* are particularly interesting examples of the change of abnormal RS-T segments and T waves in Leads II and III to normal; in one case spontaneously, and in the other after exercise.

Three of the cases had mitral stenosis. All five had normal cardiac function on exercise tests. It is emphasized that pre-excitation is associated rather frequently with organic heart disease but its prognostic significance remains uncertain. SAYEN.

Trier, M.: Penicillin Treatment of Subacute Bacterial Endocarditis. Acta Med. Scandinav. **126:**140 (Nos. II-III), 1946.

The author reports four cases and reviews the literature in part. Two patients were "cured" (five and nine month follow-ups). The two fatalities were thought at necropsy to have resulted from cardiac failure, although in one case there was still slight bacterial activity deep in the vegetations. Three to six weeks of therapy with 200 to 300 thousand units of penicillin daily is considered adequate for most cases. Since only small quantities of the drug are available in Denmark the author recommends that it be reserved for patients who do not have signs of advanced heart damage, particularly failure associated with aortic valve destruction, in order to minimize the number of those who die of congestive failure after a bacteriologic "cure."

SAYEN.

Altschul, Rudolf: Experimental Cholesterol Arteriosclerosis. Arch. Path. **42:**277 (Sept.), 1946.

The writer was the first to study the reaction of skeletal muscle to experimental cholesterol arteriosclerosis. Rabbits, guinea pigs, and golden hamsters were placed on a diet of powdered egg yolk and yeast to produce an ample degree of experimental cholesterol arteriosclerosis. Three types of changes were noted in skeletal muscle: (1) waxy hyaline degeneration of the sarcoplasm; (2) basophilic granular degeneration of the sarcoplasm with infiltration of calcium salts in which the muscle nuclei did not disappear, but were liberated from the diseased sarcoplasm and were sufficiently proliferated to form a distinctive accumulation of cells; and (3) a survival of basophilic sarcoplasm, but with the fibers remaining very thin and the nuclei proliferating in longitudinal nuclear rows.

Altschul admits that none of the above changes are specific for experiments with cholesterol feeding, since they occur under many circumstances, the most important of which may be regarded as nutritional myodegeneration. There is one change in skeletal muscle which he regards as specific for cholesterol arteriosclerosis; namely, transformation of muscle nuclei into foam cells. He points out that foam cells have never been found in skeletal muscle except under conditions of experimental cholesterol arteriosclerosis. He also states that these new proliferated nuclei show a distinct phagocytic activity and that the associated vascular change, lipoid arteriolosclerosis, is not directly connected with the changes in the skeletal muscle fibers. The vascular changes, per se, apparently cause no damage to the muscle tissue proper. GOULEY.

Walser, A.: The Influence of Autonomic Drugs on the T Waves in the Exercise Electrocardiogram. Cardiologia **10:**231, 1946.

The author studied the effect of exercise on the T-wave patterns of ten athletes. He found, as had other investigators, that mild exercise was followed immediately by lowered T-wave amplitude which gave way in about five minutes to a longer period of increased amplitude before the height returned to normal. Violent exercise (eight flights of stairs) caused a reversal of this order, an immediate elevation of the T waves being followed by a period of subnormal amplitude. The latter type of response was said to occur with light exercise when the subjects were poorly trained or neurasthenic.

The effect of synephrin tartrate (60 mg.) plus atropine sulfate (1.0 mg.) was to exaggerate the usual response to violent exercise in the electrocardiogram. A combination of physostigmine salicylate (1.0 mg.) and ergotamine tartrate (0.5 mg.) reduced the amount of T-wave flattening somewhat. The author believes that the effect of an increase of sympathetic tone was to reduce and the effect of increased vagal tone to increase the T-wave amplitude, at least in the post-exertional phase in athletes undergoing violent exercise. LENEL.

Reveno, W. S.: Thiouracil in Angina Pectoris. Am. J. Medicine **1**:607 (Dec.), 1946.

Eight patients with angina pectoris were given an initial daily dose of 0.6 to 0.4 Gm. of thiouracil until some improvement was noted. The dose was then reduced to 0.3 to 0.2 Gm. daily. Nitroglycerin and sedatives were permitted as needed. The basal metabolic rate was determined at two-week intervals at first, and later at four-week intervals.

In two patients who failed to remain under observation for longer than six weeks and three months, respectively, no improvement was noted. A third patient, observed for two months, reported improvement. In these three patients the reduction in basal metabolic rate varied between —3 and —14 per cent.

The remaining five patients, who were observed for six to eight months, usually demonstrated improvement in symptoms by the end of the second month of treatment. The drop in the basal metabolic rates of these patients varied between 7 and 29 per cent.

Two patients developed symptoms and signs of myxedema. Another patient developed joint pains and headache on the sixth day of treatment, which necessitated temporary interruption of therapy for one week. Upon resuming the drug at a reduced dosage level no further difficulty was experienced until the eighth month when the thyroid became diffusely enlarged. A fourth patient experienced temporary gastric distress.

Substitution of 75 to 125 mg. of propyl-thiouracil in one patient did not satisfactorily maintain the improvement that had been obtained with thiouracil. However, two patients were successfully maintained on 100 mg. of propyl-thiouracil for three months, after improvement had been obtained on thiouracil.

After cessation of thiouracil four of five patients remained improved for one to four months.

No changes occurred in the electrocardiograms of any patient while on thiouracil.

FRIEDLAND.

Scarlini, F.: Rupture of a Chronic Fibrous Aneurysm of the Interventricular Septum Cuore e Circ. **30**:89 (July-August), 1946.

A clinical case is reported where a chronic fibrous aneurysm of the interventricular septum due to coronary heart disease ruptured into the right ventricle. The patient, a 71-year-old woman, suddenly complained of precordial pain and appeared to be in shock. Low grade fever, leucocytosis, and an increased sedimentation rate were noted. A loud systolic murmur and a systolic thrill were present over the precordium. The electrocardiogram showed high P waves in Lead II and general signs of coronary heart disease. The x-ray revealed an enlargement of the cardiac silhouette with displacement of the lower right arch (enlargement of the right ventricle) and deformity of the left border with absence of pulsations near the apex.

The clinical diagnosis was that of recent infarction with subsequent rupture of the interventricular septum. Death occurred twelve days later. The autopsy showed that no recent infarction existed but that a recent perforation of a very fibrotic septum had occurred. The author considers that the absence of typical changes of acute infarction in the electrocardiogram should permit a correct diagnosis when the clinical picture is that of rupture of the septum.

LUISADA.

Castleman, B., and Bland, E. F.: Organized Emboli of the Tertiary Pulmonary Arteries. Arch. Path. **42**:581 (Dec.), 1946.

The authors report a case of a white woman, 44 years of age, who, following pregnancy nine years before, became progressively cyanotic. At the age of 36 she had sharp intermittent pain

substernally and in the epigastrium, lasting from a few minutes to several hours; soon thereafter she developed effort dyspnea. Examination at that time revealed orthopnea, some cyanosis without clubbing of the fingers. There were no heart murmurs, but the second pulmonic sound was loud, and right axis deviation and large P waves were seen in the electrocardiogram. Fluoroscopically, there was enlargement of the right ventricle and pulmonary conus without auricular enlargement. The patient developed progressive right heart failure with venous distention, enlargement of the liver, and leg edema. The lungs remained clear throughout the entire illness. Acute general peritonitis was the terminal event.

Necropsy revealed marked dilatation and hypertrophy of the right auricle and ventricle, with a small left ventricle. The coronary arteries and the aorta were normal. In contrast, the pulmonary artery showed marked atherosclerosis of all of its main branches, with occlusion in all tertiary branches by tough fibrous trabecular formations attached to the intima and associated with thrombosis in various stages of organization. There was marked elastosis in the walls of these occluded branches and also in the trabecular channels filling the lumina. Distal to these points of occlusion, the walls of the small branches of the pulmonary artery were normally thin and completely free from atheroma. The picture was that of organized and recanalized thrombi. The interesting thing in this case, different from all other reported cases of pulmonary arteriosclerosis, was the fixed and predictable site for the development of occlusion. Small pleural fibrous plaques were present which were believed to be the result of previous infarctions. The veins of the legs and pelvis were not examined.

It is the belief of the writers that the widespread obstruction in the tertiary branches was the result of some previous pelvic operation, with pelvic vein thrombosis and a secondary shower of emboli throughout the lungs but with lodgment sufficiently proximal to the pleura to allow collateral circulation to function and develop, thus preventing infarction in the mid- and central portions of the lungs. GOULEY.

Wheeler, E. O., Bridges, W. C., and White, P. D.: Diet Low in Salt (Sodium) in Congestive Heart Failure. J.A.M.A. **133**:16 (Jan. 4), 1947.

The mechanism of the production of edema in heart failure may be dependent on several factors, such as the retention of sodium, increased hydrostatic pressure, and, in some cases, a decrease in colloid osmotic pressure due to low serum proteins. Of these, the retention of sodium is one of the most important and at the same time one of the easiest to treat.

The regimen adapted was a low sodium diet (1.5 to 2.0 Gm. per day) which yielded a neutral ash. Fluids were allowed as desired up to 3 liters per day. Most of the patients were given ammonium chloride, mercurial diuretics, and digitalis as required.

Fifty patients were selected in whom previous treatment had yielded unsatisfactory results; either their dyspnea and edema were not controlled, or the control of these symptoms required the use of mercurial diuretics at too frequent intervals. The duration of treatment ranged from one month to one and a half years; the average was seven months.

Four of the patients were unable to follow the diet satisfactorily. The remainder cooperated and maintained a satisfactory restriction of sodium. In eleven patients the results could not be evaluated for various reasons. Of the remaining thirty-five patients, twenty-two showed improvement. Eighteen of twenty patients with hypertensive and/or coronary heart disease showed improvement, and in nine of these the improvement was marked. Of the four remaining patients whose heart disease was of miscellaneous etiology, three showed improvement. In general, patients with coronary and hypertensive heart disease responded much better than did patients with rheumatic heart disease.

These authors advocate the more widespread use of the sodium diet in the treatment of congestive failure. BELLET.

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